

5.01 DACTYLIS GLOMERATA with POA PRATENSIS, LOLIUM PERENNE, ANTHOXANTHUM ODORATUM and PHLEUM PRATENSE, 100 IR tablet: sublingual, 3 + 300 IR tablet: sublingual, 28; 300 IR tablet: sublingual, 30, Oralair®, Stallergenes Australia Pty Ltd

1. Purpose of Application

1.1 The submission requested an Authority Required (Streamlined) PBS listing of a sublingual form of allergen immunotherapy containing Dactylis glomerata with Poa pratensis with Lolium perenne with Anthoxanthum odoratum and Phleum pratense (which will be referred to by the trade name Oralair®) for the treatment of moderate to severe allergic rhinitis/rhinoconjunctivitis caused by grass pollen.

2. Requested listing

2.1 The submission requested the following new listing:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
DACTYLIS GLOMERATA + POA PRATENSIS + LOLIUM PERENNE + ANTHOXANTHUM ODORATUM + PHLEUM PRATENSE 100IR sublingual tablet, 3 300 IR sublingual tablet, 28	1	0	\$ [REDACTED]	Oralair® Stallergenes
Category / Program	GENERAL – General Schedule			
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives			
Condition:	Grass pollen allergic rhinitis			
PBS indication:	Grass pollen allergic rhinitis			
Treatment phase:	Initial treatment			
Restriction:	Authority required (STREAMLINED)			
Treatment criteria:	Must be initiated by a specialist physician			

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Clinical criteria	<p>Patient must have moderate to severe allergic rhinitis, defined as the presence of one or more of the following symptoms: Impairment of sleep Impairment of daily activities, leisure or sport Impairment of school or work Troublesome symptoms, AND Patient must have a documented history of clinically relevant symptoms to temperate grasses, AND Patient must have a positive cutaneous test and/or a positive titre of the specific IgE to the grass pollens Meadow (Poa pratensis L.), Cocksfoot (Dactylis glomerata L.), Rye (Lolium perenne L.), Sweet vernal (Anthoxanthum odoratum L.) or Timothy (Phleum pratense L.), AND Patient must be not properly controlled or intolerant to symptomatic treatments: patient must have had an inadequate response to standard medical management for allergic rhinitis, in particular inadequate response after antihistamines and nasal corticosteroids have been trialled for one pollen season.</p>
Population criteria:	Patient must be an adult, adolescent or child above the age of 5 years.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
DACTYLIS GLOMERATA + POA PRATENSIS + LOLIUM PERENNE + ANTHOXANTHUM ODORATUM + PHLEUM PRATENSE 300IR sublingual tablet, 30	1	6	\$ [REDACTED]	Oralair® Stallergenes

Category Program	/ GENERAL – General Schedule
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Grass pollen allergic rhinitis
PBS indication:	Grass pollen allergic rhinitis
Treatment phase:	Continuing treatment
Restriction:	Authority required (STREAMLINED)
Treatment criteria:	If no clinical benefit has been achieved after 12 months, treatment should be discontinued.
Clinical criteria:	Patient must have previously been issued with a streamlined authority prescription for this drug.
Population criteria:	Patient must be an adult, adolescent or child above the age of 5 years.

2.2 Listing was requested on a cost-effectiveness basis compared with placebo.

2.3 The submission assumed a treatment duration of approximately eight months per year, which includes four months of pre-seasonal treatment and four months of co-seasonal treatment. The requested listing is designed for this case, with an initial treatment phase of one month (including initiation dosing of 100-300IR over the first three days), followed by a continuing phase for seven months. The ESC noted there was uncertainty around the appropriate duration of each course of treatment on a per patient basis, as it could be influenced by several environmental factors such as length of the pollen season, geography and climate (humid versus arid). Accordingly a shorter script coverage period may be more appropriate to allow tailoring of treatment to varying pollen season durations. The Pre-Sub-Committee Response (PSCR) acknowledged the potential complexity of the proposed restriction, and

stated that the sponsor is willing to work with relevant stakeholders to resolve any issues.

- 2.4 DUSC considered the requested restriction wording may permit usage beyond the intended population with moderate to severe allergic rhinitis. The areas of concern identified by DUSC were:
- the symptoms described in the restriction (such as troublesome symptoms) were generalised and could apply to a broad range of people.
 - the minimum reaction or titre level should be specified.
 - while the restriction requires that the patient must have an inadequate response after antihistamines and nasal corticosteroids have been trialled for 12 months, the time frame of 12 months could be interpreted as consecutive or non-consecutive months.
 - the proposed PBS restriction does not preclude Oralair® being initiated part way through the pollen season if a patient presents with symptoms despite symptomatic treatment, which is inconsistent with the clinical evidence.
- 2.5 The PBAC noted the Australasian Society of Clinical Immunology and Allergy (ASCIA) recommended that sublingual allergen immunotherapy should be continued for a period of three years. ASCIA recommended that allergen immunotherapy be initiated by specialists in clinical immunology and allergy and yearly or twice-yearly specialist review is recommended to assess efficacy, compliance, side effects and benefits. ASCIA further advised that assessment of benefit in clinical practice is largely based on an assessment of frequency and severity of symptoms, reduced requirement for symptomatic treatments and quality of life measures. More objective measurements of benefit (e.g. nasal airway flow) are not available in routine clinical practice in Australia.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3. Background

- 3.1 TGA status at time of PBAC consideration: Oralair® was TGA registered on 28 April 2011 for the treatment of grass pollen allergic rhinitis with or without conjunctivitis in adults, adolescents and children (above the age of five years) with clinically relevant symptoms, confirmed by a positive cutaneous test and/or a positive titre of the specific IgE to the grass pollen.
- 3.2 Oralair® has not previously been considered by the PBAC.

4. Clinical place for the proposed therapy

- 4.1 Allergic rhinoconjunctivitis is a common chronic inflammatory illness in both adults and children, characterised by the presence of rhinorrhoea, nasal congestion, sneezing, nasal and ocular pruritus (itching) and watery eyes. The most common causative allergens include pollens, dust mites, moulds, and insects. Untreated or inadequately treated allergic rhinoconjunctivitis may cause sleep disturbance, daytime fatigue and depressed mood, irritability, and behavioural problems.

- 4.2 The ESC noted that there are no other items for the treatment of allergic rhinitis due to grass pollen currently listed on the PBS. The ESC noted the advice from the Department that the PBAC previously recommended the delisting of nasal sprays for the treatment of rhinitis and rhinorrhea conditions (such as, sneezing, itchy nose, and runny nose). The PBAC indicated that for many patients the benefits of these products are relatively small and PBS outlays may be better directed towards management of more severe diseases. The ESC further noted the advice from the Department that no items for these indications have been on the PBS since 1 November 2000.¹
- 4.3 The submission claimed that Oralair® would be used as a treatment option after failure of standard pharmacotherapy, including antihistamines, and nasal and oral corticosteroids.
- 4.4 The ESC noted the intended positioning of allergen immunotherapy as last-line treatment in the clinical algorithm. However, the ESC considered that as no other treatments for this indication are currently available on the PBS, listing this agent might result in Oralair® being prescribed earlier in the treatment algorithm. DUSC also considered Oralair® may be used earlier in the treatment algorithm due to the potential disease-modifying effects. As allergic rhinitis is a symptom-driven issue and can be long-term, this may contribute to some use beyond the requested restriction. The pre-PBAC response highlighted differences in terms of the mechanism of action and the duration of treatment effect between allergen immunotherapies and first-line treatments involving antihistamines and corticosteroids.
- 4.5 The PBAC noted advice received from ASCIA clarifying the use of Oralair® in clinical practice. The PBAC specifically noted the advice that “the 5 grass mix in Oralair®, Alustal and Staloral is a mixture of temperate (northern European) grasses of the pooideae (often referred to in Australia as the ryegrass) family. The ryegrass family is one of the most prolific producers of pollen in Australia. Some patients with allergic rhinitis in the southern temperate areas of Australia are predominantly or solely sensitised to pollens produced by the ryegrass family and are likely to benefit from these products. However, many patients in southern Australia and most patients in northern tropical or subtropical parts of Australia are also sensitised to subtropical grasses such as Bermuda, Bahia and Johnson, which are dominant in central and northern areas. The allergens in the pollens of these grasses have only limited cross-reactivity with those of the ryegrass family; therefore allergen immunotherapy extracts containing solely 5-grass mix such as Oralair® may be less effective in these patients.”

For more detail on PBAC’s view, see section 7 “PBAC outcome”

¹ 2000-01 Health and Aged Care Budget Papers, The Commonwealth Budget, [Budget Paper No. 2 - Budget Measures 2000-01](#). Accessed 6 June 2016.

5. Comparator

- 5.1 The submission nominated placebo as the main comparator on the basis that there are no other PBS listed therapies for the treatment of allergic rhinitis due to grass pollen.
- 5.2 The submission also presented a supplementary comparison of subcutaneous immunotherapies (SCIT) and sublingual immunotherapies (SLIT) containing all five of the grass pollen allergens contained in the Oralair® SLIT.
- 5.3 The evaluation considered that alternative grass pollen allergen immunotherapies, such as Alustal (SCIT containing all five of the grass pollen allergens contained in Oralair®) and Staloral® (SLIT containing all five of the grass pollen allergens contained in Oralair®), may be the therapies most likely to be replaced by Oralair® in practice. Utilisation estimates presented in the submission suggest that the vast majority of patients who would use Oralair® if listed on the PBS would switch from these therapies. Symptomatic treatments such as oral antihistamines and nasal corticosteroids may also be replaced by Oralair® if it were to be listed on the PBS. However, as none of the currently available therapies have been assessed by the PBAC for efficacy, safety and cost-effectiveness, the placebo comparison was also considered informative.
- 5.4 The ESC considered that it would have been informative if the submission had provided a direct comparison of Oralair® and SCITs and symptomatic treatments. The ESC considered that the use of SCITs are not uncommon in Australian clinical practice and would likely be replaced by the listing on the PBS of a SLIT due to the difference in the mode of administration and potential reduced safety concerns of a tablet (compared with injection). The ESC noted patients currently receiving SCITs, such as Alustal, may have severe allergies to a range of common allergens (not just limited to grass pollen).

For more detail on PBAC's view, see section 7 "PBAC outcome"

6. Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and discussed the natural history of the disease, how the drug would be used in practice, and addressed other matters in response to the Committee's questions.
- 6.2 The PBAC considered that the hearing provided a clinical perspective on treating this disease, particularly in the approach specialists take with treating patients with this condition and current prescribing practices with allergen immunotherapies. The PBAC noted the advice that the grasses in the sublingual tablet are temperate grasses which are mainly distributed in the southern regions of Australia. The clinician indicated that the drug may not be effective for grass pollen allergy sufferers in the northern tropical and subtropical regions of Australia (which the clinician indicated may extend as far south as Sydney). The clinician noted that it would be

unlikely for allergen immunotherapies to be prescribed as first-line therapy for allergic rhinitis caused by grass pollen allergens in clinical practice.

- 6.3 The PBAC noted that for patients with severe cases of allergic rhinitis caused by grass pollen, the clinically relevant symptoms usually include blocked nose, daytime somnolence and swollen eyes. In terms of the more severe presentations of allergic rhinitis, the PBAC noted that patients would have a reduced quality of life; in children this can impact on their ability participate fully in educational activities at school and in adults the severity of symptoms may prevent them from having a productive working life.

Consumer comments

- 6.4 The PBAC noted and welcomed the input from Allergy & Anaphylaxis Australia (A&AA). The comments described a range of benefits of treatment with allergen immunotherapies including the lessening of the overall burden allergic rhinitis on the patient including the impact on their quality of life. The comments noted the cost of Oralair® and other immunotherapies put these products out of reach for many patients. The A&AA noted the ubiquity of grass pollens and the difficulty this poses with managing the condition. The A&AA further noted the benefits arising from the ease and convenience of administration of a sublingual tablet compared with an injection.

Clinical trials

- 6.5 The submission was based on four head-to-head trials comparing Oralair® to placebo as a treatment for moderate to severe allergic rhinitis (VO34.04, VO52.06, VO53.06 and VO61.08).
- 6.6 A published meta-analysis was provided as evidence of equivalent effectiveness between subcutaneous and sublingual routes of administration for grass pollen immunotherapy (Nelson et al., 2015).
- 6.7 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Oralair® randomised trials		
VO34.04	Randomised, double-blind, placebo-controlled, multi-national, multi-centre, 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.	Clinical study report. 6 June 2006.
	Didier A, Malling H-J, Worm M, Horak F, Jaeger S, Montagut A, et al. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis.	<i>Journal of Allergy and Clinical Immunology</i> . 2007;120(6):1338-45.
	Horak F, Jaeger S, Worm M, Melac M, Didier A. Implementation of pre-seasonal sublingual immunotherapy with a five-grass pollen tablet during optimal dosage assessment.	<i>Clinical and Experimental Allergy</i> . 2009;39(3):394-400.
	Malling H-J, Montagut A, Melac M, Patriarca G, Panzner P, Seberova E, et al.	<i>Clinical and</i>

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Trial ID	Protocol title/ Publication title	Publication citation
	Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in patients with different clinical profiles of allergic rhinoconjunctivitis.	<i>Experimental Allergy</i> . 2009;39(3):387-93.
VO52.06	<p>A randomised, double-blind, placebo-controlled, multi-national, multi-centre, Phase III paediatric study of the efficacy and safety of 300 IR sublingual immunotherapy (SLIT) administered as allergen-based tablets once daily to children suffering from grass pollen rhinoconjunctivitis.</p> <p>Halken S, Agertoft L, Seidenberg J, Bauer C-P, Payot F, Martin-Munoz MF, et al. Five-grass pollen 300IR SLIT tablets: Efficacy and safety in children and adolescents.</p> <p>Vereda A, Halken S, Melac M, Le GM, Wahn U. 5-grass pollen 300IR SLIT tablets: Efficacy and safety in children and adolescents.</p> <p>Wahn U, Tabar A, Kuna P, Halken S, Montagut A, de Bo, et al. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis.</p>	<p>Clinical study report. 24 April 2008.</p> <p><i>Pediatric Allergy and Immunology</i>. 2010;21(6):970-6.</p> <p><i>Pediatric Allergy and Immunology</i>. 2009;20:1.</p> <p><i>Journal of Allergy and Clinical Immunology</i>. 2009;123(1):160-6.</p>
VO53.06	<p>A randomised, double-blind, placebo-controlled, multi-national, multi-centre, Phase III study to assess the long term efficacy, carry-over effect and safety of two dosing regimens of 300 IR sublingual immunotherapy (SLIT) administered as allergen-based tablets once daily to patients suffering from grass pollen rhinoconjunctivitis.</p> <p>A randomised, double-blind, placebo-controlled, multi-national, multi-centre, Phase III study to assess the long term efficacy, carry-over effect and safety of two dosing regimens of 300 IR sublingual immunotherapy (SLIT) administered as allergen-based tablets once daily to patients suffering from grass pollen rhinoconjunctivitis</p> <p>Didier A, Malling HJ, Worm M, Horak F, Sussman GL. Prolonged efficacy of the 300IR 5-grass pollen tablet up to 2 years after treatment cessation, as measured by a recommended daily combined score</p> <p>Didier A, Malling H-J, Worm M, Horak F, Sussman G, Melac M, et al. Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis.</p> <p>Didier A, Worm M, Horak F, Sussman G, de Bo, Le GM, et al. Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis.</p>	<p>Clinical study final summary report. 24 July 2013</p> <p>Clinical study interim report (years 1 to 4). 16 December 2011</p> <p><i>Clinical and Translational Allergy</i>. 2015;5:12.</p> <p><i>Clinical and Experimental Allergy</i>. 2013;43(5):568-77.</p> <p><i>Journal of Allergy and Clinical Immunology</i>. 2011;128(3):559-66.</p>
VO61.08	<p>Stallergenes S.A. (2012). A randomized, double-blind, placebo-controlled, multicentre, phase III study of the efficacy and safety of 300 IR sublingual immunotherapy (SLIT) administered as allergen-based tablets once daily to adult patients suffering from grass pollen rhinoconjunctivitis.</p> <p>Cox LS, Casale TB, Nayak AS, Bernstein DI, Creticos PS, Ambroisine L, et al. Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: The importance of allergen-specific serum IgE.</p>	<p>Clinical study report. 25 January 2012.</p> <p><i>Journal of Allergy and Clinical Immunology</i>. 2012;130(6):1327-34.</p>
Meta-analysis of direct randomised trials		
Serrano et al. (2014)	Serrano, E., Wahn, H. U., Didier, A., & Bachert, C. (2014). 300IR 5-Grass pollen sublingual tablet offers relief from nasal symptoms in patients with allergic rhinitis.	<i>American Journal of Rhinology and Allergy</i> , 28(6), 471-476
Subcutaneous immunotherapy vs. sublingual immunotherapy (meta-analysis)		

Trial ID	Protocol title/ Publication title	Publication citation
Nelson et al (2015)	Nelson, H., Cartier, S., Allen-Ramey, F., Lawton, S. and Calderon, M. A. (2015). Network meta-analysis shows commercialized subcutaneous and sublingual grass products have comparable efficacy	<i>J Allergy Clin Immunol Pract</i> 3(2): 256-266.e253

- 6.8 The ESC noted that the trials were limited to patients allergic to grass pollen only and this might not necessarily be reflective of patients with severe allergic rhinitis who are also allergic to a wide range of other allergens. The pre-PBAC response clarified that the Oralair® trials were not restricted to mono-sensitised patients; 17-29% of patients also had a positive skin prick test to dust mites and 20-37% to birch pollen across trials.
- 6.9 An additional trial, VO60.08, was identified but not included. The submission claimed this was due to a shorter pre-seasonal treatment period in this trial (two months) compared with the four month pre-seasonal treatment used in the other trials presented and in the requested PBS listing. However, in clinical practice it is unlikely that treatment will perfectly adhere to this period and thus the results of this trial may still be useful. The ESC noted that in clinical practice, the pre-seasonal treatment period may be a less than 4 months in some treatment naive patients, as they may not seek treatment until they start experiencing symptoms.
- 6.10 The key features of the direct randomised trials are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Primary outcome	Use in modelled evaluation
Oralair® vs. placebo						
VO34.04	284	MC, R, DB, PC One pollen season	Low	Adults with moderate to severe allergic rhinoconjunctivitis	Average rhinoconjunctivitis symptom score (ARcTSS)	RcTSS Symptom controlled days RQLQ
VO52.06	266	MC, R, DB, PC One pollen season	Low	Children (5-17 years) with moderate to severe allergic rhinoconjunctivitis	Average rhinoconjunctivitis symptom score (ARcTSS)	RcTSS Medication free days RQLQ
VO53.06	393	MC, R, DB, PC Three pollen seasons with two years of follow up	Low	Adults with moderate to severe allergic rhinoconjunctivitis	Average adjusted symptom score	RcTSS Symptom controlled days RQLQ
VO61.08	438	MC, R, DB, PC One pollen season	Low	Adults with moderate to severe allergic rhinoconjunctivitis	Daily combined score	RcTSS Symptom controlled days RQLQ
Subcutaneous immunotherapy vs. sublingual immunotherapy (meta-analysis)						
Nelson et al. (2015)	37 studies; 7759 patients	Used SMD to describe symptom scores and rescue medication; included some subgroup analyses				Equivalence of SLIT/SCIT

DB, double blind; MC, multi-centre; R, randomised; PC, placebo controlled; ARcTSS, average rhinoconjunctivitis total symptom score; RcTSS, rhinoconjunctivitis total symptom score; RQLQ, rhinoconjunctivitis quality of life questionnaire; SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy; SMD, standardised mean difference.

Source: compiled during the evaluation

Comparative effectiveness

- 6.11 Table 3 summarises the mean difference in average rhinoconjunctivitis total symptom score (ARcTSS) during the pollen season between Oralair® and placebo across randomised trials. The ARcTSS for a given day is defined as the sum of the six individual symptom scores (sneezing, rhinorrhoea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes), each measured on a scale of 0-3 (0= no symptoms; 3=severe symptoms).

Table 3: Results of mean difference in ARcTSS between Oralair® and placebo across the direct randomised trials (FAS)

Trial	Oralair®		Placebo		LS mean difference (95% CI)	Relative LS mean difference (%)
	N	LS mean (SD)	N	LS mean (SD)		
VO34.04 (Primary outcome)						
Y1	136	3.58 (2.98)	148	4.93 (3.23)	-1.39 (-2.09, -0.69)	-27.4
VO52.06 (Primary outcome)						
Y1	131	3.25 (2.86)	135	4.51 (2.93)	-1.13 (-1.80, -0.46)	-28.0
VO53.06 (Secondary outcome)						
Y1	188	4.49 (3.35)	205	4.97 (3.35)	-0.48 (-1.04, 0.08)	-9.6
Y2	160	3.22 (3.52)	172	4.42 (3.61)	-1.20 (-1.83, -0.56)	-27.1
Y3	149	2.67 (3.63)	165	4.03 (3.71)	-1.37 (-2.03, -0.71)	-33.9
Y4	143	3.07 (3.91)	155	3.89 (3.97)	-0.82 (-1.55, -0.09)	-21.0
Y5	127	2.90 (3.90)	133	3.49 (3.90)	-0.59 (-1.37, 0.19)	-16.9
VO61.08 (Secondary outcome)						
Y1	208	3.64 (4.53)	228	4.58 (4.52)	-0.94 (-1.58, -0.30)	-20.5
Pooled Year 1 result from random effects meta-analysis I²=22%					-1.00 (-1.41, -0.59)	-

Source: Table B.6.4 p. 96 of the submission

Notes: Average rhinoconjunctivitis total symptom score ranges from 0-18, with 18 representing most severe symptoms across six symptoms.

Abbreviations: CI, confidence interval; SD, standard deviation; LS, least squares; FAS, full analysis set.

- 6.12 Although results were variable across studies, the pooled result showed that on average treatment with Oralair® was associated with an improvement of 1 point on the average rhinoconjunctivitis total symptom score (on a scale of 0-18). The point estimate met the minimal clinically important difference (MCID) nominated in the submission (≥ 1 point improvement in symptom scores). However, the ESC considered that the absolute difference was small compared with the overall scale (0-18) and that the lower confidence limit for the pooled result was an improvement of just 0.59 of a point.
- 6.13 In the longer term study VO53.06, Oralair® demonstrated statistically significant reductions in symptom scores compared with placebo in Years 2-4, but differences in Year 5 were not statistically significantly different from placebo.
- 6.14 Results for the proportion of symptom controlled days, where patients experienced no rhinoconjunctivitis symptoms and took no rescue medication, are summarised in Table 4.

Table 4: Results of mean difference in percentage of symptom controlled days between Oralair® and placebo across the direct randomised trials (FAS)

Trial	Oralair®		Placebo		Mean difference (95% CI)	p-value
	N	Mean % (SD)	N	Mean % (SD)		
VO34.04 (Exploratory outcome)						
Y1	136	25.3% (30.2)	148	14.9% (23.6)	NR	0.0006
VO53.06 (Secondary outcome)						
Y1	188	18.6% (24.9)	205	17.4% (27.5)	NR	0.2874
Y2	160	31.9% (34.8)	172	20.1% (28.7)	NR	0.0015
Y3	149	37.9% (37.0)	165	26.4% (31.9)	NR	0.0030
Y4	143	36.0% (38.2)	155	25.6% (32.3)	NR	0.0713
Y5	127	35.7% (36.3)	133	29.3% (33.3)	NR	NR
VO61.08 (Secondary outcome)						
Y1	210	27.9% (32.7)	228	21.1% (29.7)	NR	0.0285
Meta-analysis of Year 1 results I²=60%					5.91 (0.60, 11.21)	0.03

Source: Table B.6.3, p.94 of the submission

Notes: Symptom controlled days are days during the pollen season where the rhinoconjunctivitis total symptom score (RcTSS) = 0 and the rescue medication score (RMS) = 0.

Abbreviations: CI, confidence interval; SD, standard deviation; LS, least squares; FAS, full analysis set.

- 6.15 The pooled results showed that treatment with Oralair® was associated with statistically significantly more symptom controlled days compared with placebo. With an average duration of pollen season of approximately 2 months across the trials, this translates to an additional 3.5 days in which symptoms were controlled without rescue medication. There was considerable unexplained heterogeneity between studies.
- 6.16 In the longer-term trial VO53.06, the difference between groups was not statistically significant in year 1, but Oralair® was associated with statistically significantly more symptom-free days compared with placebo in years 2-3. Statistical significance was lost by year 4. The ESC considered the year 4 result as indicative of a waning of treatment benefit attributed to patients being off-treatment.
- 6.17 The proportions of days in which rescue medication was used in the trials are summarised in Table 5.

Table 5: Results of mean difference in proportion of days any rescue medication was used between Oralair® and placebo across the direct randomised trials (FAS)

Trial	Oralair®		Placebo		Mean difference (95% CI)	p-value
	N	Mean % (SD)	N	Mean % (SD)		
VO34.04 (Secondary outcome)						
Y1	136	19.7% (24.8)	148	27.9% (29.3)	NR	0.0194
VO52.06 (Secondary outcome)						
Y1	131	35.4% (33.2)	135	46.5% (34.6)	NR	0.0146
VO53.06 (Secondary outcome)						
Y1	188	35.1% (32.6)	205	45.1% (33.8)	NR	0.0006
Y2	160	24.7% (29.1)	172	40.1% (32.4)	NR	<0.0001
Y3	149	19.6% (26.8)	165	29.4% (29.6)	NR	<0.0001
Y4	143	24.1% (29.3)	155	32.0% (31.3)	NR	0.0121
Y5	127	25.4% (30.5)	133	32.1% (31.0)	NR	0.0643
VO61.08 (Secondary outcome)						
Y1	208	9.1% (15.5)	228	16.1% (24.5)	NR	0.0200
Meta-analysis of Year 1 results I²=0%					-8.21 (-10.95, -5.46)	<0.00001

Source: Table B.6.5, p. 97 of the submission.

Abbreviations: CI, confidence interval; SD, standard deviation; LS, least squares; FAS, full analysis set; NR, not reported.

- 6.18 The pooled result suggested that treatment with Oralair® results in a statistically significant reduction in use of rescue medication compared with placebo. With an average pollen season duration of approximately 2 months in the trials, this translates to approximately 5 additional days where rescue medication use was avoided.
- 6.19 In the longer term trial VO53.06, Oralair® was associated with statistically significantly less use of rescue medication compared to placebo in years 1-4, but the difference between groups in year 5 was not statistically significant.
- 6.20 The submission presented a MCID developed by the World Allergy Organisation which recommended a percent reduction in the active versus placebo group, where treatment should be associated with a reduction at least 20% greater than placebo to scores that incorporate both symptom levels and rescue medication use. The ESC noted the PSCR proposed an alternative MCID of 15% relative reduction in combined symptom and rescue medication score compared with placebo, with a 95% CI lower bound of at least -10% (which was specified by the FDA for sublingual immunotherapy, and applies only to the average combined score, see Table 7 below). The evaluation noted that while the combined scores are useful for registration purposes to detect a treatment effect, in clinical practice treatment effect will be determined based on whether an appreciable reduction in symptoms has been achieved regardless of whether it was achieved using immunotherapy or symptomatic treatments.
- 6.21 Both of the nominated MCIDs are relative measures and should be interpreted with caution. The group differences reported in the included trials are small relative to the overall scale, and are likely to represent only a small clinical benefit. The general 20% margin from the World Allergy Organisation is problematic as it may not adequately account for differences in outcome measures (number of symptoms, scoring scale for severity of symptoms) or patient characteristics (such as baseline severity). The 15% margin for the average combined score (symptom and medication scores) is difficult to interpret because the two outcome measurements are calculated using different scales which abstracts the individual symptom and medication scores.

The symptom score is the sum of severity scores (0 = absent, 1 = mild, 2=moderate, 3=severe) across six different symptoms (sneezing, rhinorrhoea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes). The score assigned to rescue medication is arbitrary (1=antihistamine, 2=nasal corticosteroid, 3=oral corticosteroid) and thus should not be treated as interval data. Finally, relying on percentage improvement between treatment and placebo to determine clinical effectiveness fails to take into account the range of the symptom scales, which would provide a better indication of clinical effectiveness.

- 6.22 The results of mean difference in the average adjusted symptom score (AASS; Table 6) are reproduced below.

Table 6: Results of mean difference in AASS between Oralair® and placebo across the direct randomised trials (FAS)

Trial	Oralair®		Placebo		LS mean difference (95% CI)	Relative LS mean difference (%)
	N	LS mean (SD)	N	LS mean (SD)		
VO53.06 (Primary outcome)						
Y1	188	5.74 (4.36)	205	6.99 (4.37)	-1.25 (-1.98, -0.53)	-17.9
Y2	160	4.03 (4.31)	172	5.92 (4.43)	-1.89 (-2.67, -1.11)	-31.9
Y3	149	3.39 (4.36)	165	5.21 (4.47)	-1.82 (-2.61, -1.02)	-34.9
Y4	143	3.85 (4.96)	155	5.00 (4.81)	-1.14 (-2.03, -0.26)	-22.9
Y5	127	3.86 (4.79)	133	4.51 (4.80)	-0.65 (-1.60, 0.31)	-14.3
VO61.08 (Secondary outcome)						
Y1	208	3.98 (4.99)	228	5.22 (4.97)	-1.24 (-1.94, -0.53)	-23.7
Meta-analysis of Year 1 results I²=0%					-1.25 (-1.88, -0.61)	-

Source: Table B.6.1 p.91 of the submission

Note: The average adjusted symptom score represents the RcTSS adjusted for rescue medication use and ranges from 0-18. A higher score represents greater severity of symptoms and medication use.

Abbreviations: CI, confidence interval; SD, standard deviation; LS, least squares; FAS, full analysis set.

- 6.23 Across both studies, the AASS was statistically significantly lower in the Oralair® treatment group than the placebo group. However, the absolute differences are small compared with the overall scale (0-18). The meta-analysis of Year 1 data from the trials resulted in a difference in least squares means of -1.25 (95% CI: -1.88, -0.61).
- 6.24 The results of trial VO61.08, and trial VO53.06 for years 2-4 met the nominated MCID of a 20% relative difference or greater compared to placebo; the MCID was not met for year 1 of trial VO53.06.
- 6.25 The results for the mean difference in average combined score (CS; Table 7) with additional calculation of crude confidence intervals for the relative least square mean percent difference is presented below.

Table 7: Results of mean difference in average combined score between Oralair® and placebo across the direct randomised trials (FAS)

Trial	Oralair®		Placebo		LS mean difference (95% CI)	Relative LS mean percent difference (crude 95% CI)
	N	LS mean (SD)	N	LS mean (SD)		
VO52.06 (Secondary outcome)						
Y1	131	0.57 (0.43)	135	0.77 (0.48)	-0.19 (-0.30, -0.09)	-26.0 (-39.0, -11.7)
VO53.06 (Secondary outcome)						
Y1	188	0.67 (0.48)	205	0.79 (0.47)	-0.11 (-0.19, -0.03)	-14.3 (-24.1, -3.8)
Y2	160	0.44 (0.48)	172	0.66 (0.50)	-0.22 (-0.30, -0.13)	-32.6 (-45.5, -19.7)
Y3	149	0.38 (0.49)	165	0.57 (0.50)	-0.19 (-0.28, -0.10)	-33.8 (-49.1, -17.5)
Y4	143	0.44 (0.53)	155	0.57 (0.54)	-0.13 (-0.22, -0.03)	-22.5 (-38.6, -5.3)
Y5	127	0.41 (0.53)	133	0.52 (0.53)	-0.11 (-0.2, 0.00)	-20.7 (-38.5, 0.0)
VO61.08 (Secondary outcome)						
Y1	208	0.37 (0.48)	228	0.50 (0.48)	-0.13 (-0.19, -0.06)	-25.2 (-38.0, -12.0)
Meta-analysis of Year 1 results I²=0%					-0.14 (-0.20, -0.09)	-20.8 (-29.7, -13.4)

^a In trial VO34.04, the CS was calculated differently to the other trials with a different scale (CSR text, Section 9.7.1.6.3, p.49), thus it was excluded in the pooled meta-analysis.

Source: Table B.6.2, p. 93 of the submission.

Notes: The combined score takes into account the patient's daily RctSS and RMS by adding them, assuming equivalent importance of symptoms and medication scores. The CS ranges from 0-3, with a higher score indicating greater severity of symptoms and medication use. Confidence intervals (in italics) for the relative LS mean difference calculated by evaluator and are approximate only. Point estimate for meta-analysed relative LS mean difference calculated by evaluator and is approximate only.

Abbreviations: CI, confidence interval; SD, standard deviation; LS, least squares; FAS, full analysis set.

- 6.26 Across all studies, the average combined score was statistically significantly lower in the Oralair® treatment group than the placebo group. However, the absolute differences are small compared to the overall scale (0-3). The meta-analysis of Year 1 data from the trials resulted in a difference in least squares means of -0.14 (95% CI: -0.20, -0.09).
- 6.27 The results of trials VO52.06 and VO61.08, and trial VO53.06 for years 2-4 met the nominated MCID of a 20% relative difference or greater compared to placebo; the MCID was not met for year 1 of trial VO53.06.
- 6.28 For the MCID presented in the PSCR of ≥15% improvement compared with placebo, and an upper bound of the 95% confidence interval of ≤10%, the MCID was met for trials VO52.06 and VO61.08 and trial VO53.06 for years 2-3; the MCID was not met for years 1, 4 and 5 of trial VO53.06. The MCID was met for the crude meta-analysis of the relative LS mean percent difference calculated during the evaluation.
- 6.29 Overall the ESC considered the study results were difficult to interpret and the effect size was uncertain in terms of whether this translated to clinically meaningful benefits to patients.
- 6.30 The submission presented the results of a network meta-analysis by Nelson et al. (2015) comparing the effectiveness of SLIT with SCIT over one pollen season in patients with grass pollen allergic rhinoconjunctivitis. Both SLITs and SCITs significantly reduced symptom and medication scores compared to placebo. The network meta-analysis showed no significant differences in standardised mean difference for symptom scores or medication scores between subcutaneous and sublingual tablet immunotherapies. The assessed therapies were not limited to

Oralair®, Alustal® and Staloral®. The comparison was performed only on data from the first pollen season after treatment initiation, with no comparison provided for longer-term performance. There was considerable inconsistency among outcomes used in the included trials to measure symptoms and medication use, limiting the comparison to the use of the standardised mean difference to describe outcome scores.

Comparative harms

- 6.31 In the trials, Oralair® was associated with a higher incidence of treatment-related adverse events compared with placebo. The majority of adverse events were mild to moderate in intensity and were consistent with the known profile of allergen immunotherapy. The most commonly reported side effects were oral pruritus, mouth oedema and itchy throat. The high rates of administration site symptoms may affect treatment compliance, and may partly offset the benefits of the reduction in rhinitis symptoms. Although rare, post-marketing data suggests that treatment with Oralair® may be associated with severe laryngopharyngeal disorders.
- 6.32 The meta-analysis by Nelson et al. (2015) used in the submission to compare the effectiveness of SLIT and SCIT for grass pollen allergic rhinitis did not compare the safety of the two routes of administration. Another recent meta-analysis of SCIT and SLIT with grass allergens for seasonal allergic rhinitis (Di Bona et al. 2012) showed on average 0.86 treatment-emergent adverse events were reported per patient who received SCIT, less than one-half of those receiving SLIT (2.13 adverse events/patient). Across both SCIT and SLIT, most adverse events were modest in severity for both the treatment and placebo groups. The withdrawal rate for adverse events was higher in the SLIT group (78 patients; 0.04%) than in the SCIT group (18 patients; 0.019%). In the trials included in the meta-analysis there were 12 episodes of anaphylaxis that required adrenaline of the 960 patients treated with SCIT, and only 1 episode of the 4046 patients treated with SLIT.

Benefits/harms

- 6.33 A summary of the comparative benefits and harms for Oralair® versus placebo is presented in Table 8.

Table 8: Summary of comparative benefits and harms for Oralair® and placebo

Benefits						
Trial	Oralair®		Placebo		LS Mean difference: Oralair® vs. placebo (95% CI)	
	n	LS Mean (SD)	n	LS Mean (SD)		
Average rhinoconjunctivitis total symptom score (Year 1 results; scale 0-18, 0 represents no symptoms)						
VO34.04	136	3.58 (2.98)	148	4.93 (3.23)	-1.39 (-2.09, -0.69)	
VO52.06	131	3.25 (2.86)	135	4.51 (2.93)	-1.13 (-1.80, -0.46)	
VO53.06	188	4.49 (3.35)	205	4.97 (3.35)	-0.48 (-1.04, 0.08)	
VO61.08	208	3.64 (4.53)	228	4.58 (4.52)	-0.94 (-1.58, -0.30)	
Pooled Year 1 result from random effects meta-analysis I²=22%					-1.00 (-1.41, -0.59)	
Trial	n	Mean % (SD)	n	Mean % (SD)	Mean difference (95% CI)	
Proportion of symptom-controlled days (Year 1 results)						
VO34.04	136	25.3% (30.2)	148	14.9% (23.6)	NR	
VO53.06	188	18.6% (24.9)	205	17.4% (27.5)	NR	
VO61.08	210	27.9% (32.7)	228	21.1% (29.7)	NR	
Meta-analysis of Year 1 results I²=60%					5.91 (0.60, 11.21)	
Proportion of days any rescue medication was used (Year 1 results)						
VO34.04	136	19.7% (24.8)	148	27.9% (29.3)	NR	
VO52.06	131	35.4% (33.2)	135	46.5% (34.6)	NR	
VO53.06	188	35.1% (32.6)	205	45.1% (33.8)	NR	
VO61.08	208	9.1% (15.5)	228	16.1% (24.5)	NR	
Meta-analysis of Year 1 results I²=0%					-8.21 (-10.95, -5.46)	
Harms						
	Oralair®	Placebo	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Oralair®	Placebo	
Most frequently reported drug-related treatment-related events						
Oral pruritus						
VO34.04	40/155	8/156	5.03 (2.44, 10.40)	25.8	5.1	21% (13, 28)
VO52.06	45/139	2/139	22.50 (5.57, 90.94)	32.4	1.4	31% (23, 39)
VO53.06	87/207	25/219	3.68 (2.46, 5.50)	42.0	11.4	31% (23, 39)
VO61.08	57/233	11/240	5.34 (2.87, 9.92)	24.5	4.6	20% (14, 26)
Meta-analysis	229/734	46/754	5.36 (3.18, 9.03)	31.2	6.1	25% (19, 31)
Throat irritation						
VO34.04	14/155	4/156	3.52 (1.19, 10.46)	9.0	2.6	6% (1, 12)
VO52.06	11/139	7/139	1.57 (0.63, 3.94)	7.9	5.0	3% (-3, 9)
VO53.06	47/207	8/219	6.22 (3.01, 12.84)	22.7	3.7	19% (13, 25)
VO61.08	53/233	4/240	13.65 (5.02, 37.11)	22.7	1.7	21% (15, 27)
Meta-analysis	125/734	23/754	4.67 (1.92, 11.35)	17.0	3.1	12% (3, 21)
Mouth oedema						
VO34.04	7/155	0/156	15.10 (0.87, 262.06)	4.5	0	5% (1, 8)
VO52.06	18/139	0/139	37.00 (2.25, 607.98)	12.9	0	13% (7, 19)
VO53.06	20/207	3/219	7.05 (2.13, 23.38)	9.7	1.4	8% (4, 13)
VO61.08	0/233	0/240	NE	0	0	0% (-1, 1)
Meta-analysis	45/734	3/754	9.73 (3.48, 27.21)	6.1	0.4	6% (-6.2, 18.9)

Source: Compiled during the evaluation

* Median duration of treatment: VO34.04 184-186 days; VO52.06, 179-181 days; VO53.06, Year 1 166-167 days; VO60.08, 179.8 days.

Abbreviations: RD, risk difference; RR, risk ratio; NR, not reported; NE, not estimable

- 6.34 On the basis of the meta-analysed results of the clinical trials presented in the submission, Oralair® compared with placebo resulted in:
- A reduction in symptoms as measured by the average total rhinoconjunctivitis symptom score, of 1.0 on the 18-point symptom scale. A one point reduction in the symptom score represents a reduction in the severity of one of six allergic rhinitis symptoms from severe to moderate, moderate to mild, or mild to no symptoms;
 - A 6% increase in the number of days in which allergic rhinitis symptoms were controlled without the use of symptomatic treatments (e.g. oral antihistamines, nasal corticosteroids). With an average duration of pollen season of approximately 2 months across the trials, this translates to an additional 3.5 symptom controlled days;
 - An 8% reduction in the number of days where symptomatic treatments (e.g. oral antihistamines, nasal corticosteroids) were used. With an average pollen season duration of less than 2 months in the trials, this translates to approximately 5 additional days where rescue medication use was avoided.
 - Approximately 25 additional patients experiencing oral pruritus (oral itch) for every 100 patients treated;
 - Approximately 14 additional patients experiencing throat irritation for every 100 patients treated; and
 - Approximately 6 additional patients experiencing mouth oedema (swollen mouth) for every 100 patients treated.

Clinical claim

- 6.35 The submission described Oralair® as superior to placebo in terms of efficacy, with an acceptable safety profile. The ESC considered that the efficacy claim may be reasonable in terms of symptom reduction, however the magnitude of the change associated with treatment with Oralair® over placebo was small overall. Treatment with Oralair® was most frequently associated with local application reactions such as oral pruritus, mouth oedema and throat irritation. The symptom scores measured in the trials did not account for the impact of these adverse events, and it was unclear to what extent these may offset some of the claimed benefits in terms of symptom control. In addition, the ESC considered that these adverse events may encourage poor adherence to the treatment which could result in reduced relative effectiveness of Oralair® (compared with patients who were being closely monitored in the trials). The pre-PBAC response argued that these reactions “typically occur shortly after the first dose is taken, mainly during the first month of treatment, and are generally transient in nature. Patients who can tolerate Oralair® during the first month are unlikely to experience further adverse reactions and are likely to comply with ongoing treatment.”
- 6.36 The PBAC considered that the claim of superior comparative effectiveness compared with placebo was reasonable. However, the PBAC considered that the magnitude, clinical significance and persistence of the incremental benefit over placebo was unclear.
- 6.37 The PBAC considered that grass pollen extracts were likely to be inferior in terms of comparative safety, compared with placebo.

- 6.38 The submission described SCITs and SLITs containing grass pollen extracts as having comparable efficacy. The ESC considered that this claim was not well supported given the issues discussed in paragraph 6.30. The submission also described SLITs as generally having a better safety profile than SCITs. The ESC noted the smaller number of episodes of anaphylaxis observed with SLITs compared with SCITs. The ESC considered that some patients may prefer the mode of administration of Oralair® (daily sublingual tablet) to a monthly subcutaneous injection but considered that the adverse events associated with Oralair® (such as mouth and throat irritation) may lead to poorer adherence to treatment, compared with SCITs.
- 6.39 The PBAC considered that the claim of comparable efficacy compared with SCITs and SLITs was not well supported.

Economic analysis

- 6.40 The submission presented a modelled cost-effectiveness analysis comparing Oralair® with placebo for the treatment of patients with moderate to severe allergic rhinoconjunctivitis.
- 6.41 A summary of the model structure and rationale is presented in Table 9.

Table 9: Summary of model structure and rationale

	Adult model	Child model
Time horizon	9 years in the model base case versus 5 years in trials	9 years in the model base case versus 7-8 months in trials
Outcomes	Rhinitis symptom adjusted life years Symptom controlled days Rhinitis quality of life questionnaire (units of improvement)	Rhinitis symptom adjusted life years Medication free days Rhinitis quality of life questionnaire (units of improvement)
Methods used to generate results	Markov cohort expected value analysis	
Cycle length	1 year with a half-cycle correction for all costs and outcomes	
Transition probabilities	Treatment persistence (Sieber 2011) Death (Australian life tables)	Treatment persistence (Sieber 2011) Death (Australian life tables) Incidence of asthma (Jacobsen 2007)
Discount rate	5% for costs and outcomes	
Software package	Excel 2010	

Source: constructed during the evaluation

- 6.42 The key issues with the economic model are summarised in Table 10.

Table 10: Key issues with the model

Description	Method/value	Impact
Time horizon	The submission assumed a sustained treatment effect of six years after three years of treatment. Clinical evidence for this effect was not presented, and this assumption was inadequately supported by the identified studies, which were mostly of low quality and had limited applicability to the PBS population.	High
Utilities	The submission mapped symptom scores (RcTSS) to unvalidated quality of life scores (rhinitis symptom utility index) in the economic model. This required several assumptions regarding the distribution of symptoms, their severity and duration that were unsupported by the clinical data. The estimated quality of life values represent scores between the best possible and worse possible allergic rhinitis states rather than the traditional bounds for utility values (perfect health and death). Model outcomes should therefore be considered rhinitis symptom adjusted life years rather than quality adjusted life years.	High
Model structure	The model was largely based on treatment states (immunotherapy with symptomatic treatments; symptomatic treatments alone), rather than health states (with the exception of the asthma state in the child model). The submission did not consider the variation in magnitude of treatment effect that could be captured by a model specific to allergic rhinitis (e.g. symptomatic/asymptomatic or mild/moderate/severe). Using the presented model structure, the submission assumed a constant treatment effect for all patients regardless of symptom severity.	Unclear
Variability in pollen season	The model structure did not allow for seasonal variability and patient response rates influenced by levels of exposure to allergens and the associated symptom presentation. Data from published literature suggests different distribution, allergen levels and duration of pollen season across Australia. The model inappropriately assumed a constant treatment effect during the three year treatment and for six years post-treatment.	Unclear
Reduction in asthma risk	The submission acknowledged that there was little evidence to support the assumption of reduced risk of asthma in adults receiving allergen immunotherapy and incorporated asthma as a health state in the child model only. The assumption that treatment with Oralair® can prevent the development of asthma in children was poorly supported based on studies of low quality and applicability.	Low to moderate
Adverse events	Based on adverse event data reported in the trials, Oralair® was associated with a higher incidence of itchy mouth, mouth swelling and throat irritation. The model did not consider the impact (e.g. cost or disutility) of these adverse events.	Unclear

Source: Constructed during the evaluation

- 6.43 The results of the adult and child economic models are summarised in Tables 11 and 12, respectively.

Table 11: Results of the economic evaluation: adult model

Component	Oralair®	Placebo	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Rhinitis symptom adjusted life years	6.131	6.041	0.090
Incremental cost per rhinitis symptom adjusted life year gained			\$ [REDACTED]

Source: Table D.5.5 p.185 of the submission

Table 12: Results of the economic evaluation: child model

Component	Oralair®	Placebo	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Rhinitis symptom adjusted life years	6.249	6.121	0.127
Incremental cost per rhinitis symptom adjusted life year gained			\$ [REDACTED]

Source: Table D.5.5 p.185 of the submission

- 6.44 Based on the adult model, treatment with Oralair® was associated with an incremental cost per rhinitis symptom adjusted life year (RSALY) gained of \$15,000 – \$45,000.
- 6.45 In the child model, treatment with Oralair® was associated with an incremental cost per RSALY gained of \$15,000 - \$45,000.
- 6.46 The lower ICER in the child model compared with the adult model was due to better symptom scores from the child trial mapped to better quality of life scores; and also offsets from the cost of asthma being included in the child model. The ESC considered that the inclusion of cost offsets associated with the prevention of asthma in the child model was inadequately supported. The ESC noted that the cost offset for asthma was not a main driver in the model; excluding this cost offset increased the cost per RSALY gained to \$15,000 - \$45,000.
- 6.47 The ESC considered that the results of the models were difficult to interpret. Given the RSALY is based on quality of life values measured on a scale from worst to best rhinitis symptoms, an incremental QALY (based on utilities measured on a scale from death to perfect health) would likely be smaller than the incremental RSALY derived in the model. As such, the incremental cost per QALY gained would likely be higher than the incremental cost per RSALY gained in the model. The ESC considered that the derived RSALYs could not be compared with QALYs.
- 6.48 The model was most sensitive to the duration of benefit following treatment and the rhinitis quality of life values based on the Rhinitis Symptom Utility Index (RSUI).
- The assumption of a sustained treatment effect over 9 years (3 years of treatment and 6 years of benefit following treatment) was not adequately supported by published evidence. The ESC considered that the assumption of continued benefit for nine years was inadequately supported, particularly given the results of the 5-year trial, VO53.06 (which had 3 years of treatment and 2 years of follow-up) suggested diminishing benefit beyond year 3. The ESC considered that benefit beyond the treatment period should be considered, but a waning of incremental benefit is likely to be more realistic. The submission presented an alternative base case for the adult model which assumed a treatment effect over 5 years (3 years of treatment and 2 years of benefit following treatment); the cost per RSALY gained for this scenario increased to \$15,000 - \$45,000.
 - The rhinitis quality of life values used in the model relied on a mapping from symptom scores to the RSUI that required several assumptions regarding the distribution of symptoms, their severity and duration, which were unsupported by the clinical data. The resulting values are not utilities, and the rhinitis adjusted life years derived cannot be compared with quality adjusted life years.
- 6.49 The persistence estimates used in the economic evaluation were based on an observational study of subcutaneous and sublingual grass allergen immunotherapies

in Germany. Estimates from this study were unreliable given the overly broad definition of persistence (at least one script per year at any time) and the assumption of perfect persistence in first year of treatment. Additionally, it was unclear whether clinical and environmental circumstances between Germany and Australia are sufficiently similar to generalise results.

- 6.50 The submission also presented a cost analysis, comparing Oralair® with Alustal® and Staloral®, two alternative allergen immunotherapies available in Australia in a limited capacity. The ESC noted that the submission did not clearly demonstrate non-inferiority and the submission did not provide an estimate of equi-effective doses of Oralair® versus Alustal® and Staloral®.
- 6.51 At the proposed DPMQ for Oralair®, Oralair® was associated with cost savings of \$██████ compared with Staloral®, due to the higher costs of Staloral® immunotherapy. Compared to Alustal®, Oralair® was associated with cost savings of \$██████, due to cost offsets from injection administration associated with Alustal®. A 12 month treatment duration was assumed for Staloral®. If an eight month treatment duration was assumed, consistent with that proposed for Oralair®, the difference in costs between Oralair® and Staloral® would be -\$██████. The submission calculated a DPMQ for all products rather than using ex-manufacturer pricing. As neither Staloral® nor Alustal® are PBS listed, a comparison at the ex-manufacturer level may have been more appropriate.

Drug cost/patient/8 month treatment course: \$██████

- 6.52 At the requested DPMQ of \$██████ for one initiation or continuation pack of Oralair® (30 days of treatment), the drug cost per patient per year was estimated to be \$██████ (assuming one initiation pack and seven continuation packs in the first year, and eight continuation packs per year in subsequent years). This assumes four months of pre-seasonal treatment and four months of co-seasonal treatment (a pollen season duration of four months). Evidence presented in the submission suggested that the duration of the pollen season in Australia is variable, and the number of packs per year may change to reflect this.
- 6.53 The ESC noted that due to the complexities associated with the requested restriction, the drug cost per patient per year could vary significantly between patients.

Estimated PBS usage & financial implications

- 6.54 This submission was considered by DUSC.
- 6.55 The submission used a mixed market share/epidemiology approach to estimate the extent of use and financial implications to government associated with the PBS listing of Oralair®. Using the updated estimates from the PSCR, at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 million.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Total all PBS Oralair patients					
(% of specialist referred population)	2.9%	4.4%	5.5%	6.6%	7.2%
Total Oralair packs (8 months of therapy)					
Estimated net cost to PBS/RPBS					
Net cost to the PBS (less copayments)	\$	\$	\$	\$	\$
Costs of GP and specialists visit and skin prick tests to government					
Additional costs for Oralair	\$	\$	\$	\$	\$
Saving from Alustal treatment avoided	-\$	-\$	-\$	-\$	-\$
Savings from Staloral treatment avoided	-\$	-\$	-\$	-\$	-\$
Total savings	-\$	-\$	-\$	-\$	-\$
Net cost to government	\$	\$	\$	\$	\$

Abbreviations: DPMQ, dispensed price for maximum quantity; GP, general practitioner; PBS, Pharmaceutical Benefits Scheme
 Source: Executive Summary of Commentary Table 11 page 15. Updated numbers from Excel spreadsheet "PSCR Section E_Oralair_final_PSCR_response" in the PSCR.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to government would be less than \$10 million per year.

- 6.56 DUSC considered the estimates presented in the submission to be underestimated. The main issues were:
- DUSC was unable to verify the estimated number of treated patients because while the submission presents epidemiological data to arrive at an eligible population, these numbers do not inform the estimated number of patients treated. The estimated number of patients treated was based on the sponsor's market data.
 - DUSC considered the place in therapy for Oralair® is unclear and that it may be used earlier in the treatment algorithm due to the potential disease-modifying effects, which may contribute to some use beyond the restriction.
 - DUSC considered a PBS listing of Oralair® would likely grow the market beyond patients switching from the private market given the large size of the eligible patient population.
 - DUSC considered that due to the varied pollen seasons throughout Australia, it is likely that some patients will use Oralair® for longer than 8 months per year.
 - The claimed cost-offsets due to the prevention of asthma and reduced GP visits for privately available subcutaneous Alustal® administration are unlikely to be realised in practice.

Quality Use of Medicines

- 6.57 DUSC considered the lack of immediate treatment effects, compared with symptomatic treatments, could result in low compliance with the treatment regimen; the clinical benefit of a shorter treatment course is unknown. Similarly, the restriction

does not preclude commencing therapy part way through the pollen season, but the clinical benefit of this is also unknown.

7. PBAC Outcome

- 7.1 The PBAC did not recommend the listing of *Dactylis glomerata* with *Poa pratensis* with *Lolium perenne* with *Anthoxanthum odoratum* and *Phleum pratense* (referred to by the trade name, Oralair®) on the PBS for allergic rhinitis due to grass pollen. In reaching this conclusion, the PBAC considered that the magnitude of clinical benefit was unclear and the cost-effectiveness of the requested listing was unknown.
- 7.2 The PBAC considered that the hearing and consumer input clarified that the appropriate and intended place in therapy for Oralair® is as later line therapy in patients with persistent moderate to severe forms of allergic rhinitis due to grass pollen – that is, after patients have tried and failed to control symptoms using symptomatic drug treatments and corticosteroids. The PBAC considered there was still a risk of leakage to patients earlier in the treatment algorithm given the lack of symptomatic treatments listed on the PBS and the generalised nature of the symptoms described in the restriction. The PBAC considered that restricting prescribers to allergen specialists may assist to ensure that only patients who are likely to benefit from therapy are prescribed Oralair®. In addition, the PBAC noted the ESC's and DUSC's concerns regarding the uncertain treatment duration given the differing lengths of the pollen season across Australia and considered the complexity of Oralair® only including temperate grass pollens.
- 7.3 The PBAC agreed with ESC that placebo was an appropriate comparator to allow the PBAC to assess the efficacy, safety and cost-effectiveness of treatment. However, the PBAC noted that Oralair® was most likely to replace other grass pollen allergen immunotherapies and therefore these were also appropriate comparators.
- 7.4 The PBAC noted that the submission excluded trial VO60.08 because of the shorter pre-seasonal treatment period used, compared with the four months in the requested PBS listing. The PBAC agreed with the ESC that the results of the trial may have been informative given that, in clinical practice, the pre-seasonal treatment period may be a less than four months in some treatment naïve patients, as they may not seek treatment until they start experiencing symptoms.
- 7.5 The PBAC considered that the primary outcome measure in VO34.04 and VO52.06 – ArCTSS (as described in paragraph 6.11) – was difficult to interpret and the MCID nominated in the submission (of a ≥ 1 point improvement) was small compared with the overall scale (0-18). The PBAC considered that the use of ArCTSS did not provide clarity as to what clinically meaningful outcomes are expected from effective treatment. The PBAC also noted the alternative MCIDs presented in the PSCR and agreed with the issues raised in paragraphs 6.20 and 6.21.
- 7.6 The PBAC considered that the results of the long term Oralair® study (VO53.06) did not provide sufficient evidence to support the claim that the treatment effect is sustained when a patient moves off treatment. In particular, the PBAC noted the

apparent waning of treatment benefit, particularly in terms of ArCTSS (Table 3), symptom controlled days (Table 4) and average adjusted symptom score (Table 6).

- 7.7 Overall, the PBAC agreed with the ESC that the study results were difficult to interpret and the effect size was uncertain in terms of whether this translated to clinically meaningful benefits to patients.
- 7.8 The PBAC noted that that Oralair® was associated with a higher incidence of adverse events compared with placebo, including oral pruritis, mouth oedema and itchy throat. The PBAC agreed with the ESC that these adverse events represent a considerable inconvenience to patients and this may have implications for patient compliance and may partly offset the benefits of the reduction in rhinitis symptoms.
- 7.9 The PBAC agreed with the ESC that the estimate of cost effectiveness was hard to interpret and uncertain for the following reasons:
- The models presented did not adequately account for the substantial variability expected in treatment effects due to variations of patient characteristics and allergen exposure (including length of pollen season). In particular, both models (children and adults) were based on treatment states rather than health states and this involved an inappropriate assumption that there was a constant treatment effect for all patients regardless of symptom severity.
 - The submission assumed a sustained and constant treatment effect of six years after three years of treatment. The clinical evidence presented in the submission (including the long-term Oralair® study, VO53.06) did not adequately support this assumption.
 - The inclusion of cost offsets associated with the prevention of asthma in the child model was inadequately supported.
 - The model did not account for adverse events which may be associated with disutility or additional financial implications.
 - The rhinitis quality of life values used in the model relied on a mapping from symptom scores to the rhinitis symptom utility index that required several assumptions regarding the distribution of symptoms, their severity and duration, which were unsupported by the clinical data. The resulting values are not utilities.
 - The submission effectively modelled outcomes in terms of RSALYs instead of QALYs and therefore the results did not allow for a comparison of cost effectiveness to other health interventions. The incremental cost per QALY gained would likely be higher than the incremental cost per RSALY gained in the model
- 7.10 The PBAC agreed with DUSC that the estimated financial implications and utilisation were uncertain and likely to be underestimated.
- 7.11 The PBAC considered that a resubmission for Oralair® would need to be a major submission.
- 7.12 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9. Sponsor's Comment

Stallergenes is committed to working with the PBAC and the Department to ensure patients with moderate to severe grass pollen induced allergic rhinitis can access Oralair through the PBS.