

**5.02 HOUSE DUST MITE AMERICAN with HOUSE DUST MITE EUROPEAN, 100 IR tablet: sublingual, 3 + 300 IR tablet: sublingual, 28; 300 IR tablet: sublingual, 30; Actair®, Stallergenes Australia Pty Ltd**

**1 Purpose of Application**

1.1 The submission requested an Authority Required (STREAMLINED) listing for a sublingual form of allergen immunotherapy containing house dust mite American with house dust mite European (which will be referred to by the trade name Actair®) for the treatment of allergic rhinitis caused by house dust mites.

**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
HOUSE DUST MITE ALLERGEN EXTRACT 100IR sublingual tablet, 3 300IR sublingual tablet, 28	1	0	\$ [REDACTED]	Actair® Stallergenes

<b>Category / Program</b>	GENERAL – General Schedule
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Condition:</b>	House dust mite allergic rhinitis
<b>PBS Indication:</b>	House dust mite allergic rhinitis
<b>Treatment phase:</b>	Initial treatment
<b>Restriction:</b>	Authority required (STREAMLINED)
<b>Treatment criteria:</b>	Must be initiated by a specialist physician.
<b>Clinical criteria:</b>	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 house dust mite; AND Patient must have a positive cutaneous test and/or a positive titre of the specific IgE to one of the house dust mites: American ( <i>D. farinae</i> ) or European ( <i>D. pteronyssinus</i> ); 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 trialed for 12 months.
<b>Population criteria</b>	Patient must be an adult or adolescent above the age of 12 years.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
HOUSE DUST MITE ALLERGEN EXTRACT 300IR sublingual tablet, 30	1	5	\$ [REDACTED]	Actair® Stallergenes
<b>Population criteria</b>	Patient must be an adult or adolescent above the age of 12 years.			
<b>Treatment phase: continuing treatment</b>				
<b>Condition</b>	House dust mite allergic rhinitis			

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 or adolescent above the age of 12 years.

- 2.2 The listing was requested on a cost-effectiveness basis compared with placebo.
- 2.3 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. Further, as these therapies are available without a prescription, this could be interpreted as medically supervised or non-medically supervised therapy.
- 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: The submission was made under the TGA/PBAC Parallel Process. Actair® was approved by the TGA for 'the treatment of house dust mite allergic rhinitis with or without conjunctivitis, in adults and adolescents over 12 years diagnosed with house dust mite allergy' on 5 April, 2016. All relevant documents were available during the evaluation.
- 3.2 The PBAC has not previously considered house dust mite allergen extracts.

### **4 Clinical place for the proposed therapy**

- 4.1 House dust mite allergens are a common cause of perennial allergic rhinitis in Australia. Untreated or inadequately treated allergic rhinitis 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 dust 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.<sup>1</sup>
- 4.3 The submission positioned house dust mite allergen extracts as a last line therapy for patients who have an inadequate response to, or are intolerant of symptomatic treatments, including nasal corticosteroids and antihistamines.
- 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 Actair® being prescribed earlier in the treatment algorithm. DUSC considered the place in therapy for Actair® is unclear and Actair® 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.

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

## **5 Comparator**

- 5.1 The submission nominated placebo as the main comparator on the basis that there are no other PBS listed therapies for treatment of allergic rhinitis due to house dust mites.
- 5.2 The submission also presented a supplementary comparison with Acarizax, an alternative sublingual tablet formulation of house dust mite allergens, on the basis that it is currently in the process of obtaining TGA registration. Supplementary comparisons with the privately marketed house dust mite allergen therapies Alustal and Staloral were also presented.

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

- 5.3 The evaluation considered that alternative house dust mite allergen immunotherapies, such as Alustal and Staloral, may be the therapies most likely to be replaced by Actair®. Symptomatic treatments such as oral antihistamines and nasal corticosteroids may also be replaced by Actair® if 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 comparison of Actair® versus subcutaneous allergen immunotherapies. The ESC considered that the use of subcutaneous allergen immunotherapies are not uncommon in Australian clinical practice and would likely be replaced by the listing on the PBS of sublingual allergen immunotherapies due to the difference in the mode of administration and potential reduced safety concerns of taking a tablet (compared with injection) of taking a tablet versus an 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 dust).

*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 of specialists take with treating patients with this condition and current prescribing practices with allergen immunotherapies. The clinician noted that it would be unlikely for allergen immunotherapies to be prescribed as first-line therapy for allergic rhinitis caused by house dust mite allergens in clinical practice.
- 6.3 The PBAC noted that for patients with severe cases of allergic rhinitis caused by house dust mite, the clinically relevant symptoms usually include a year-round blocked nose. 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 existing immunotherapies put these products out of reach for many patients. The A&AA noted the difficulty of minimising exposure to dust mite allergens as a strategy

for 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 two head-to-head randomised trials comparing house dust mite allergen extract to placebo (VO57.07, 1207d1731).
- 6.6 Details of the trials presented in the submission are provided in Table 1.

**Table 1: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trials</b>		
VO57.07	A randomised, double-blind, placebo-controlled, multi-national Phase II / III study of the safety and efficacy of two doses of sublingual immunotherapy (SLIT) administered as allergen-based tablets once daily to adult patients suffering from house dust mite allergic rhinitis.	Internal study report 27 April 2012
	Bergmann KC, Demoly P, Worm M, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis.	Journal of Allergy and Clinical Immunology 2014; 133(6):1608-1614.e1606
1207d1731	A Phase 2/3 Study of S-524101 in Patients with Perennial Allergic Rhinitis.	Internal study report 26 March 2014
VO64.08	A randomised, double-blind, placebo-controlled, multinational, Phase III trial to assess the efficacy and safety of 300 IR sublingual immunotherapy (SLIT) administered as allergen-based tablets once daily to adolescents and children above the age of 5 years, suffering from house dust mite allergic rhinitis.	Internal study report 20 November 2012
	Halken S, Wahn U, Mélac M, et al. O17-Assessment of efficacy and safety of sublingual tablets of house dust mite allergen extract in children and adolescents with allergic rhinitis.	Clinical and Translational Allergy 2014; 4:17
VO67.10	A randomized, double-blind, placebo-controlled, dose ranging Phase II study to assess the efficacy and safety of 100 IR, 300 IR and 500 IR sublingual tablets of House Dust Mite allergen for the treatment of allergic rhinitis in an Environmental Exposure Chamber model.	Internal study report 13 January 2014
<b>Supplementary randomised trial</b>		
MT-06	Demoly P, Emminger W, Rehm D, et al. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized, double-blind, placebo-controlled phase III trial.	Journal of Allergy and Clinical Immunology 2016; 137(2):444-451.e448
<b>Meta-analysis of direct randomised trials</b>		
Calderon et al. (2015)	Calderon MA, Kleine-Tebbe J, Linneberg A, et al. House Dust Mite Respiratory Allergy: An Overview of Current Therapeutic Strategies.	The Journal of Allergy and Clinical Immunology: In Practice (2015); 3(6):843-855

Source: Table B.2.3, pp49-51 of the submission; Table 1.2, pp44-45 of Attachment 4 of the submission. Abstracts relating to conference proceedings omitted.

- 6.7 The ESC noted that the trials were limited to patients allergic to house dust mites 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 claimed that the effectiveness of Actair® is similar among mono- and poly-sensitised patients.

- 6.8 The submission inappropriately excluded an additional study of Actair® versus placebo in children aged 5-17 (VO64.08), on the basis that the symptom scores in both treatments arms were too low to detect a difference between groups after 12 months. Given that there was substantial overlap with the PBS population, the trial was of good quality, and baseline symptom scores were similar to those reported in VO57.07, exclusion was not considered appropriate.
- 6.9 The key features of the randomised trials are summarised in Table 2.

**Table 2: Key features of the included evidence**

Trial	N	Design/duration	Risk of bias	Patient population	Key outcome	Use in modelled evaluation
<b>Actair® vs placebo</b>						
VO57.07	509	R, DB, MC, PG, PC, 12 months (with 12 month follow-up period)	Low	18-50 years with HDM-related AR for at least 1 year	Average adjusted symptom score	Average rhinitis total symptom score <sup>1</sup>
1207d1731	968	R, DB, MC, PG, PC, 12 months	Low	12-65 years with HDM-related AR for at least 2 years	Average adjusted symptom score	Not used
VO64.08	471	R, DB, MC, PG, PC, 12 months (with 6 month follow-up period) <sup>2</sup>	Low	5-17 years with HDM-related AR for at least 1 year	Average adjusted symptom score	Not used
<b>Acarizax® vs placebo</b>						
MT-06	992	R, DB, MC, PG, PC, 12 months	Low	18-65 years with HDM-induced AR for at least 1 year	Total combined rhinitis score	Not used

Source: compiled during the evaluation

Abbreviations: R, randomised, DB, double blind; MC, multicentre; PG, parallel group; PC, placebo controlled; HDM, house dust mite; AR, allergic rhinitis;

<sup>1</sup> Average rhinoconjunctivitis total symptom score was not reported in the clinical study report. The sponsor provided post hoc data for this outcome.

<sup>2</sup> Trial VO64.08 was terminated after 18 months.

- 6.10 There were differences in access to rescue medications across the trials. Rescue medications were provided to patients for use only when the symptoms were severe or intolerable in trials VO57.07 and VO64.08, and only when symptoms interfered with daily activities in trial 1207d1731. The use of symptomatic therapies is likely to be higher in the PBS population, and therefore the treatment benefit with Actair® may be lower than reported in the clinical trials.
- 6.11 The clinical trials were conducted in Europe (VO57.07, VO64.08, MT-06) and Japan (1207d1731). Differences in the prevalence of house dust mite species between Europe and Japan affected the exchangeability of the trials. Actair® has not been evaluated in Australian conditions.
- 6.12 The use of symptomatic treatments was unrestricted in the Acarizax trial MT-06, whereas VO57.07 restricted medication use to severe or intolerable symptoms. As a

result, trial MT-06 may not be sufficiently exchangeable with the Actair® trials for indirect comparison.

### Comparative effectiveness

- 6.13 Table 3 summarises the results for the average rhinitis total symptom score for Actair® and placebo across the randomised trials. The rhinitis total symptom score (RTSS) for a given day is defined as the sum of the four rhinitis individual symptom scores (sneezing, rhinorrhoea, nasal pruritus and nasal congestion). The average RTSS (ARTSS) is an average of the daily (non-missing) RTSS during the evaluation period.

**Table 3: ANCOVA for the average rhinitis total symptom score (ARTSS)<sup>1</sup> across the direct randomised trials**

Trial ID	Actair®		Placebo		LS mean difference (95% CI)	Relative LS mean difference (%)
	N	LS mean (SD)	N	LS mean (SD)		
<b>VO57.07 (Adults)</b>						
Y1	141	2.71 (2.11)	153	3.33 (2.14)	-0.62 (-1.06, -0.17)	-18.5
Y2	132	2.60 (2.29)	137	3.13 (2.26)	-0.53 (-1.02, -0.03)	-16.8
<b>1207d1731 (Adults/adolescents)</b>						
Y1	315	6.48 (5.20)	316	7.79 (5.17)	-1.31 (-1.85, -0.77)	-16.8
<b>VO64.08 (Adolescents/children)</b>						
Y1	222	2.38 (0.13)	221	2.44 (0.13)	-0.06 (-0.40, 0.28)	-2.6
<b>Random effects meta-analysis of VO57.07 and 1207d1731, Year 1</b>					<b>SMD (95% CI)</b>	
					<b>I<sup>2</sup>=0%</b>	<b>-0.26 (-0.39, -0.13)</b>

Source: Table B.6.1, pp84-85 of the submission; Table 14.2.1.1a, p. 412 of VO64.08 clinical study report.

Abbreviations: LS, least squares; AASS, adjusted average symptom score; SE, standard error; CI, confidence interval; Y1, Year 1; Y2, Year 2.

<sup>1</sup> The average adjusted symptom score (AASS) is calculated by adjusting the rhinitis symptom score for rescue medication use and was scored from 0-12 for trials VO57.07 and VO64.08, and 0-15 for trial 1207d1731. A higher AASS is associated with a greater number and/or severity of symptoms.

- 6.14 Actair® was associated with statistically significant reductions in symptom scores compared with placebo at the end of Year 1 in trials VO57.07 and 1207d1731. The results for Year 2 (treatment free period) in trial VO57.07 were also statistically significant. However, the clinical importance of the achieved reductions was unclear, as there is no recognised MCID for this outcome. Differences in the methods used to score the RTSS between trials VO57.07 and 1207d1731, and differences in access to rescue medications across trials mean that the results of the pooled analysis should be interpreted with caution. Trial VO64.08 reported no statistically significant difference between treatment groups in symptom scores at the end of Year 1.
- 6.15 Table 4 summarises the results for the proportion of symptom controlled days for Actair® and placebo across the randomised trials.

**Table 4: Results for the proportion of symptom controlled days<sup>1</sup> across the direct randomised trials**

Trial ID	Actair®		Placebo		Mean difference (95% CI)
	N	Mean % (SD)	N	Mean % (SD)	
<b>VO57.07 (Adults)</b>					
Y1	141	25.7% (30.8)	153	18.5% (27.5)	7.21 (NR)
Y2	132	26.8% (34.7)	137	18.4% (29.7)	8.39 (NR)
<b>1207d1731 (Adults/adolescents)</b>					

Y1	315	3.6% (17.8)	316	3.9% (17.8)	-0.2 (-2.61, 2.21)
<b>VO64.08 (Adolescents/children)</b>					
Y1	212	24.8% (31.9) <sup>2</sup>	221	28.1% (32.4) <sup>2</sup>	-3.38 (NR)

Source: Table B.6.4, p.88 of the submission; Table 14.2.2.6.1a, p.833 of the VO64.08 clinical study report

Abbreviations: SD, standard deviation; CI, confidence interval; Y1, Year 1; Y2, Year 2.

<sup>1</sup> Symptom controlled days are days where rhinitis total symptom score is 0 and no rescue medication is used. The proportion of symptom controlled days was the percentage of symptom controlled days during the primary efficacy period.

<sup>2</sup> Least squares mean

- 6.16 For trial VO57.07, Actair® was associated with a higher proportion of symptom controlled days compared with placebo at the end of Year 1 (treatment period) and Year 2 (treatment free period), although confidence intervals were not reported, and the statistical significance of the results could not be assessed. Trial 1207d1731 showed no statistically significant difference between groups in the proportion of symptom controlled days. Trial VO64.08 showed a mean difference of 3.4% in favour of placebo, although the results of statistical significance tests were not available.
- 6.17 The results for the proportion of symptom controlled days were inconsistent across trials. This is likely to be due to differences between trials in the use of rescue medications. As the definition for the proportion of symptom controlled days required a rhinitis total symptom score of 0 and no rescue medication to have been used, the results may not be applicable to the proposed PBS population, who have unrestricted access to symptomatic treatments.
- 6.18 The ESC noted that the differences in improvement of symptom scores between treatment and placebo groups were low and this may potentially influence a clinician's decision to prescribe Actair® as an adjunct to other allergen immunotherapies. The ESC noted the short duration of the studies and lack of follow-up data may mask any drop-off effect that could arise when a patient ceases treatment.
- 6.19 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 incorporating 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 therapy, and applies only to the average combined score, see Table 6 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.
- 6.20 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 organisations 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.

- 6.21 The results of mean difference in the average adjusted symptom score (AASS; Table 5) are reproduced below.

**Table 5: ANCOVA for the average adjusted symptom score (AASS) across the direct randomised trials**

Trial ID	Actair®		Placebo		LS mean difference (95% CI)	Relative LS mean difference (%)
	N	LS Mean (SE)	N	LS Mean (SE)		
<b>VO57.07 (Adults)</b>						
Y1	141	3.18 (0.22)	153	3.87 (0.22)	-0.69 (-1.25, -0.14)	-17.9
Y2	132	3.04 (0.23)	137	3.67 (0.23)	-0.62 (-1.20, -0.05)	-17.0
<b>1207d1731 (Adults/adolescents)</b>						
Y1	315	5.00 (0.21)	316	6.11 (0.21)	-1.11 (-1.50, -0.72)	-18.2
<b>VO64.08 (Adolescents/children)</b>						
Y1	222	2.85 (0.16)	221	2.84 (0.16)	0.01 (-0.41, 0.43)	0.4
<b>Random effects meta-analysis of VO57.07 and 1207d1731, Year 1 I<sup>2</sup>=0%</b>					<b>SMD (95% CI)</b>	
					-0.28 (-0.41, -0.15)	

Source: Table B.6.1, pp84-85 of the submission; Table 14.2.1.1a, p. 412 of VO64.08 clinical study report.

Abbreviations: LS, least squares; AASS, adjusted average symptom score; SE, standard error; CI, confidence interval; Y1, Year 1; Y2, Year 2.

Notes: The average adjusted symptom score (AASS) is calculated by adjusting the rhinitis symptom score for rescue medication use and was scored from 0-12 for trials VO57.07 and VO64.08, and 0-15 for trial 1207d1731. A higher AASS is associated with a greater number and/or severity of symptoms.

- 6.22 The AASS was statistically significantly lower in the Actair® treatment group than the placebo group in the 1207d1731 (Japanese study) and V057.07 (European study) trials. However, the absolute differences are small compared with the overall scale (0-18). The meta-analysis of Year 1 data from these trials resulted in a standardised mean difference of -0.28 (95% CI: -0.41, -0.15). The results of the excluded V064.08 trial (children and adolescent study) did not reach statistical significance.
- 6.23 None of the trial results met the nominated MCID of a 20% relative difference or greater compared to placebo.
- 6.24 The results for the mean difference in average combined score (CS; Table 6) with additional calculation of crude confidence intervals for the relative least square mean percent difference is presented below.

**Table 6: ANCOVA for the average combined score (ACS) across the direct randomised trials**

Trial ID	Actair®		Placebo		LS mean difference (95% CI)	Relative LS mean percent difference (crude 95% CI)
	N	LS Mean (SD)	N	LS Mean (SD)		
<b>VO57.07 (Adults)</b>						
Y1	141	0.46 (0.46)	153	0.58 (0.45)	-0.07 (-0.17, 0.02)	-12.9 (-29.3, 3.4)
Y2	132	0.44 (0.41)	137	0.53 (0.41)	-0.10 (-0.18, -0.01)	-18.1 (-34.0, -1.9)

1207d1731 (Adults/adolescents)						
Y1	315	0.62 (0.52)	316	0.77 (0.50)	-0.15 (-0.201, -0.096)	-19.3 (-26.1, -12.5)
VO64.08 (Adolescents/children)						
Y1	222	0.48 (SE 0.027)	221	0.45 (SE 0.026)	0.03 (-0.04, 0.10)	7.0 (-8.9, 22.2)
<b>Pooled result from random effects meta-analysis for Year 1 I<sup>2</sup>=0%</b>					<b>SMD (95% CI)</b>	
					-0.29 (-0.42, -0.16)	

Source: Table B.6.1, pp84-85 of the submission; Table 14.2.2.5.2a, p. 830 of VO64.08 clinical study report.

Abbreviations: ACS, average combined score; LS, least squares; AASS, adjusted average symptom score; SE, standard error; CI, confidence interval; Y1, year 1; Y2, Year 2.

Notes: The average combined score (ACS) is calculated from the daily rhinitis total symptom score and the rescue medication score, and was scored 0-3 in VO57.07 and VO64.08, and 0-2.875 in trial 1207d1731. A discrepancy noted in the upper confidence interval value of Study 1207d1731 between the submission (-0.01) and the clinical study report (-0.096).

- 6.25 The ACS was statistically significantly lower in the Actair® treatment group than the placebo group in the 1207d1731 (Japanese study) trial. The average combined score (ACS) results for Year 1 (treatment period) of trial VO57.07 showed no statistically significant difference, whereas in Year 2 (treatment free period), there was a statistically significant difference in favour of Actair®. The meta-analysis of Year 1 data from these trials resulted in a standardised mean difference of -0.29 (95% CI: -0.42, -0.16). The results of the excluded VO64.08 trial (children and adolescent study) favoured placebo but did not reach statistical significance.
- 6.26 None of the trial results met the nominated MCID of a 20% relative difference or greater compared to placebo.
- 6.27 The results from the 1207d1731 trial (Japanese study) appeared to meet the nominated MCID presented in the PSCR of ≥15% improvement compared with placebo, and an upper bound of the 95% confidence interval of ≤10%. Neither the VO57.07 (European study) nor the excluded VO64.08 (children and adolescent study) met the nominated margin. The evaluation considered that the results from study 1207d1731 should be interpreted with caution as the average combined score was based on different symptom and rescue medication subscales compared to other trials. It was unclear whether the MCID for average combined symptom score can be applied to these values.
- 6.28 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. The ESC noted that the longest trial ran for one year with one year of follow-up.
- 6.29 The submission included a supplementary indirect analysis comparing Actair® (VO57.07) to Acarizax (MT-06), using placebo as the common comparator. The indirect comparison of symptom scores across the trials (ARTSS in VO57.07, AR symptom score in MT-06) and the results of the rhinitis quality of life questionnaire (overall score) resulted in no statistically significant difference between treatments. However, the results of the symptom score comparison should be interpreted with caution due to differences in access to rescue medication between the trials. The submission did not nominate a non-inferiority margin for this outcome.
- 6.30 The submission presented a naïve indirect comparison of the results of two meta-analyses of placebo-controlled trials of subcutaneous immunotherapy (7 studies;

Calderon, 2008) and sublingual immunotherapy (9 studies; Radulovic, 2010) in patients with house dust mite allergies (Calderon, 2015). The outcome reported in the meta-analyses was the rhinitis symptom score. Both subcutaneous and sublingual immunotherapies were associated with statistically significant reductions in total symptoms scores compared with placebo in patients with house dust mite allergies. No formal indirect comparison was presented and the submission's claim of comparable efficacy between subcutaneous and sublingual immunotherapy was not adequately supported.

### **Comparative harms**

- 6.31 In the clinical trials, Actair® was associated with a higher incidence of treatment-related adverse events compared with placebo, with oral pruritus, mouth oedema, and itchy throat the most frequently reported. The majority of adverse events were classified as mild to moderate in intensity and were consistent with the known profile of allergen immunotherapy. The high rates of administration site symptoms may affect treatment compliance, and may partly offset the benefits of the reduction in rhinitis symptoms.
- 6.32 The safety profile for Acarizax appeared to be consistent with Actair®, with oral pruritus, throat irritation and mouth oedema being the most common adverse events related to the treatment. The indirect comparison of safety outcomes was limited by the availability of published safety data for trial MT-06.

### **Benefits/harms**

- 6.33 A summary of the comparative benefits and harms for Actair® versus placebo is presented in Table 7.

Table 7: Summary of comparative benefits and harms for Actair® and placebo

Benefits						
Average rhinoconjunctivitis total symptom score <sup>1</sup> (0 represents no symptoms)						
Trial ID	Actair®		Placebo		LS mean difference (95% CI)	
	N	LS Mean (SE)	N	LS Mean (SE)		
<b>VO57.07</b>						
Y1	141	2.71 (2.11)	153	3.33 (2.14)	-0.62 (-1.06, -0.17)	
Y2	132	2.60 (2.29)	137	3.13 (2.26)	-0.53 (-1.02, -0.03)	
<b>1207d1731</b>						
Y1	315	6.48 (5.20)	316	7.79 (5.17)	-1.31 (-1.85, -0.77)	
<b>VO64.08</b>						
Y1	222	2.38 (0.13)	221	2.44 (0.13)	-0.06 (-0.40, 0.28)	
Random effects meta-analysis of VO57.07 and 1207d1731, Year 1 I <sup>2</sup> =0%					SMD (95% CI) -0.26 (-0.39, -0.13)	
Proportion of symptom controlled days						
Trial ID	Actair®		Placebo		Mean difference (95% CI)	
	N	Mean % (SD)	N	Mean % (SD)		
<b>VO57.07</b>						
Y1	141	25.7% (30.8)	153	18.5% (27.5)	7.21 (NR)	
Y2	132	26.8% (34.7)	137	18.4% (29.7)	8.39 (NR)	
<b>1207d1731</b>						
Y1	315	3.6% (17.8)	316	3.9% (17.8)	-0.2 (-2.61, 2.21)	
<b>VO64.08</b>						
Y1	212	24.8% (31.9) <sup>2</sup>	221	28.1% (32.4) <sup>2</sup>	-3.38 (NR)	
Harms						
	Actair®	Placebo	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Actair®	Placebo	
Most frequently reported drug-related treatment-related events						
Oral pruritus						
VO57.07	51/170	6/170	8.50 (3.75, 19.28)	30.0	3.5	26% (19, 34)
1207d1731	36/322	7/322	5.14 (2.32, 11.39)	11.2	2.2	9% (5, 13)
<b>Meta-analysis</b>	87/492	13/492	8.02 (3.93, 16.34)	17.7	2.6	17% (-1%, 36%)
Throat irritation						
VO57.07	40/170	5/170	8.00 (3.24, 19.78)	23.5	2.9	21% (14, 27)
1207d1731	66/322	12/322	5.50 (3.03, 9.98)	20.5	3.7	17% (12, 22)
<b>Meta-analysis</b>	106/492	17/492	6.16 (3.75, 10.13)	21.5	3.5	18% (14, 22)
Mouth oedema						
VO57.07	21/170	1/170	21.00 (2.86, 154.36)	12.4	0.6	12% (7, 17)
1207d1731	67/322	1/322	67 (9.36, 479.71)	20.8	0.3	20% (16, 25)
<b>Meta-analysis</b>	88/492	2/492	37.80 (9.31, 153.46)	17.9	0.4	16% (8, 25)

Source: Compiled during the evaluation.

Abbreviations: LS, least squares; SE, standard error; CI, confidence interval; Y1, Year 1; Y2, Year 2; SMD, standardised mean difference; SD, standard deviation; NR, not reported; RR, relative risk; RD, risk difference.

<sup>1</sup> Scored 0-12 for VO57.07/VO64.08 and 0-15 for 1207d1731

<sup>2</sup> Least squares mean

6.34 On the basis of the evidence presented in the submission for Actair® compared to placebo resulted in:

- An average reduction in symptoms, as measured by the rhinitis total symptom score of between 0.62 (on a scale of 0 to 12) as measured in trial VO57.07, to 1.31 (on a scale of 0 to 15) in trial 1207d1731. A 1 point reduction in symptom scores represents a reduction in the severity of one of four symptoms (sneezing, rhinorrhoea, nasal congestion, nasal pruritus) from severe to moderate, moderate

to mild, or mild to no symptoms. No difference between Actair® and placebo was found in trial VO64.08.

- Mixed results for the proportion of days in which allergic rhinitis symptoms were controlled without the use of symptomatic treatments (e.g. oral antihistamines, nasal corticosteroids) in the three trials. Trial VO57.07 found an increase in symptom controlled days of 7.2%; 1207d1731 found no difference between treatments and trial VO64.08 found a reduction in symptom controlled days of 3.4% for Actair® compared with placebo.
- Approximately 9 to 26 additional patients experiencing oral pruritus (itchy mouth) for every 100 patients treated.
- Approximately 17 to 21 additional patients experiencing throat irritation for every 100 patients treated.
- Approximately 12 to 20 additional patients experiencing mouth oedema (swollen mouth) for every 100 patients treated.

### **Clinical claim**

- 6.35 The submission described Actair® as superior in terms of comparative efficacy over placebo, with an acceptable safety profile. The ESC did not consider the claim to be well supported. There are no well-established MCIDs for the assessed outcomes, and the modest reductions achieved in symptom scores may not be clinically significant. Treatment with Actair® was most frequently associated with local application site reactions, such as oral pruritus, mouth oedema and throat irritation. The ESC considered that these adverse events may encourage poor adherence to the treatment which could result in reduced relative effectiveness of Actair® (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 Actair 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 was not adequately supported by the data. In addition, the PBAC considered that the magnitude, clinical significance and persistence of an incremental benefit over placebo was unclear.
- 6.37 The PBAC considered that Actair® was likely to be inferior in terms of comparative safety, compared with placebo.
- 6.38 The submission described Actair® as non-inferior to Acarizax® in terms of comparative efficacy and safety. The claim was not adequately supported. Differences in the methods used to score symptoms and medication use between trials, as well as differences in access to symptomatic treatments, mean the trials were likely to be insufficiently exchangeable for indirect comparison.
- 6.39 The ESC considered that some patients may prefer the mode of administration of Actair® (daily sublingual tablet) to a monthly subcutaneous injection but considered that the adverse events associated with Actair® (such as mouth and throat irritation) may encourage poorer adherence to treatment compared with SCITs.

- 6.40 The PBAC considered that the claim of non-inferiority in terms of comparative efficacy and safety between Actair® and Acarizax® was not well supported.

**Economic analysis**

- 6.41 The submission presented a modelled cost-effectiveness analysis comparing Actair® with placebo for the treatment of patients with moderate to severe allergic rhinitis.
- 6.42 A summary of the model structure and rationale is presented in Table 8.

**Table 8: Summary of model structure and rationale**

	<b>Adult model</b>	<b>Child model</b>
Time horizon	9 years in the model base case versus one year of treatment and one year of follow-up in VO57.07	9 years in the model base case versus one year of treatment and one year of follow-up in VO57.07 (based on adult data)
Outcomes	Rhinitis symptom adjusted life years Symptom controlled days Rhinitis quality of life questionnaire (units of improvement)	Rhinitis symptom adjusted life years Symptom controlled 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	

- 6.43 Key issues with the economic model are summarised in Table 9.

**Table 9: Key issues with the model**

<b>Description</b>	<b>Method/value</b>	<b>Impact</b>
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 (post hoc calculation of 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

Description	Method/value	Impact
Model structure	The model is 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
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 Actair® 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, Actair® was associated with a higher incidence of oral pruritus, mouth oedema 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

6.44 The results of the adult and child economic models are summarised in Tables 10 and 11, respectively.

6.45 **Table 10: Results of the economic evaluation: adult model**

Component	Actair®	Placebo	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Rhinitis symptom adjusted life years	5.503	5.355	0.148
<b>Incremental cost per rhinitis symptom adjusted life year gained</b>			<b>\$ [REDACTED]</b>

Source: Table D.5.5 p.168 of the submission

**Table 11: Results of the economic evaluation: child model**

Component	Actair®	Placebo	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Rhinitis symptom adjusted life years	5.543	5.385	0.157
<b>Incremental cost per rhinitis symptom adjusted life year gained</b>			<b>\$ [REDACTED]</b>

Source: Table D.5.5 p.168 of the submission

6.46 Based on the adult model, treatment with Actair® was associated with an incremental cost per rhinitis symptom adjusted life year (RSALY) gained of \$15,000 - \$45,000.

6.47 In the child model, treatment with Actair® was associated with an incremental cost per RSALY gained of \$15,000 - \$45,000.

6.48 The lower ICER in the child model compared with the adult model is due to the inclusion of cost offsets for the management of asthma which was 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 (from \$15,000 - \$45,000).

- 6.49 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.
- 6.50 The model is 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 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. The ESC noted that the longest trial ran for one year with one year of follow-up. On this basis, the ESC did not consider that there was sufficient evidence provided to assume a constant treatment effect for a total of nine years.
- 6.51 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.
- 6.52 The submission presented a cost analysis, comparing the costs of Actair® with the sublingual immunotherapy Staloral® and the subcutaneous immunotherapy Alustal®. Direct costs associated with immunotherapy, physician visits, diagnostic tests and monitoring were considered over the three year treatment duration. The ESC noted that the submission did not clearly demonstrate non-inferiority and the submission did not provide an estimate of equi-effective doses.
- 6.53 Compared with Staloral®, Actair® was associated with cost savings of \$ [REDACTED] due to the higher costs of Staloral immunotherapy. Compared to Alustal®, Actair® was associated with additional costs of \$ [REDACTED] despite the higher administration costs for Alustal®. 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/year: \$ [REDACTED]**

- 6.54 At the requested DPMQ of \$ [REDACTED] for one initiation or continuation pack Actair® (30 days of treatment), the drug cost per patient per year was estimated to be \$ [REDACTED] (assuming 1 initiation pack and 11.17 continuation packs in the first year, and 12.17 continuation packs per year in subsequent years).

**Estimated PBS usage & financial implications**

6.55 This submission was considered by DUSC.

6.56 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 Actair®. Using the updated estimates from the PSCR, at year 5, the estimated number of patients was 10,000 – 50,000 per year and the net cost to the PBS would be \$10 - \$20 million.

**Table 12: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Total all PBS Actair patients	██████	██████	██████	██████	██████
(% of specialist referred population)	8%	14%	18.1%	21.7%	24.1%
Total Actair packs (12 months of therapy)	██████	██████	██████	██████	██████
<b>Estimated net cost to PBS/RPBS</b>					
Net cost to the PBS (less copayments)	\$██████	\$██████	\$██████	\$██████	\$██████
<b>Costs of GP and specialists visit and skin prick tests to government</b>					
Additional costs for Actair	\$██████	\$██████	\$██████	\$██████	\$██████
Saving from Alustal treatment avoided	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████
Savings from Staloral treatment avoided	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████
Total savings	-\$██████	-\$██████	-\$██████	-\$██████	-\$██████
<b>Net cost to government</b>	\$██████	\$██████	\$██████	\$██████	\$██████

Abbreviations: DPMQ, dispensed price for maximum quantity; GP, general practitioner; PBS, Pharmaceutical Benefits Scheme  
 Source: Executive Summary of Commentary Table 10 page 12. Updated numbers from Excel spreadsheet "PSCR Section E\_Actair\_final\_PSCR\_response" in the PSCR

6.57 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 Actair® 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 Actair® would likely grow the market beyond patients switching from the private market given the large size of the eligible patient population.

- The claimed cost-offsets due to the prevention of asthma and reduced GP visits for privately available subcutaneous Alustal<sup>®</sup> administration are unlikely to be realised in practice.

### **Quality Use of Medicines**

- 6.58 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. DUSC also discussed the potential for non-drug treatments of allergic rhinitis (such as environmental control like vacuuming) to be overlooked in place of immunotherapy.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of house dust mite American with house dust mite European (referred to by the trade name Actair<sup>®</sup>) on the PBS for allergic rhinitis due to house dust mites. In reaching this conclusion, the PBAC considered that the magnitude of clinical benefit was unclear, and the estimate of cost-effectiveness as presented in the submission was unknown.
- 7.2 The PBAC considered that the hearing and consumer input clarified that the appropriate and intended place in therapy for Actair<sup>®</sup> is as later line therapy in patients with persistent moderate to severe forms of allergic rhinitis due to house dust mites – that is, after patients have tried and failed to control symptoms using symptomatic drug treatments, followed by the addition of 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 Actair<sup>®</sup>.
- 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 Actair<sup>®</sup> was most likely to replace other house dust mite allergen immunotherapies and these were therefore also appropriate comparators.
- 7.4 The PBAC considered that the outcome measure, average rhinitis total symptom score (ARTSS), was difficult to interpret and the MCID nominated in the submission (of a 20% improvement) was small compared with the overall scale 0-12. The PBAC considered that the use of ARTSS 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 6.19 and 6.20.
- 7.5 The PBAC considered that the results of the Actair<sup>®</sup> study VO57.07 did not provide sufficient clinical evidence to support the claim that the treatment effect is sustained when a patient moves off treatment.

- 7.6 The PBAC noted and agreed with the evaluation that it was inappropriate to exclude the results of study on children (VO64.08) as the study design was comparable with VO57.07.
- 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 Actair® was associated with a higher incidence of adverse events compared with placebo, including oral pruritus, 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. 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 did not adequately support this assumption (the longest trial provided 12 months of study plus 12 months of follow up data).
  - 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 are uncertain and likely to be underestimated.
- 7.11 The PBAC considered that a resubmission for Actair® 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**

The sponsor takes note of the PBAC's report and will review its options to ensure patients with moderate to severe house dust mite induced allergic rhinitis can have the best possible access to Actair.