

6.04 OMALIZUMAB, PRE-FILLED SYRINGE FOR SUBCUTANEOUS INJECTION, 75 MG/0.5ML, 150 MG/ML, XOLAIR®, NOVARTIS.

1 Purpose of Application

- 1.1 The submission requested a written Authority Required Section 100 (Highly Specialised Drugs Program) listing for omalizumab for treatment of severe allergic asthma in patients aged 6 to less than 12 years.

2 Proposed listing

- 2.1 The listing proposed in the submission was based on the adolescent/adult PBS restriction of omalizumab, with a few changes for the proposed paediatric population. The two key changes were:
- The required number of exacerbations in the previous 12 months was increased to at least two, compared with at least one in the adolescent/adult population. This was appropriate, as clinicians provided advice to the submission that a higher number of exacerbations would be needed before they would consider omalizumab; and
 - A criterion for adequate response to omalizumab was added in the paediatric restriction: 'a reduction in time-adjusted exacerbation rate compared with 12 months prior to baseline'. The minimum required reduction was not specified. The PBAC considered this criterion was appropriate.
- 2.2 The submission requested the same effective price as for the current restriction of omalizumab. During evaluation, a new Special Pricing Arrangement (SPA) was agreed between the Department and the Sponsor of omalizumab. Under the new agreement the effective price for omalizumab had been reduced to \$[REDACTED] for 75 mg and \$[REDACTED] for 150 mg.
- 2.3 The evaluation proposed the inclusion of a grandfathering clause in the restriction. The Pre-Sub-Committee Response (PSCR) considered that the number of paediatric patients currently treated with omalizumab for severe allergic asthma was likely to be under 10, and agreed that a grandfathering clause for these patients would be appropriate.

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

3 Background

- 3.1 **TGA status:** Omalizumab was approved for registration by the TGA for paediatric asthma in January 2016.
- 3.2 This is the first PBAC consideration for omalizumab in the paediatric population.

- 3.3 Omalizumab was first recommended for listing in November 2010 and is currently PBS-listed as a Section 100 (Highly Specialised Drugs Program) written authority required item for the treatment of adolescents and adults with uncontrolled severe allergic asthma who have failed to achieve adequate control despite optimised asthma therapy, have a total serum immunoglobulin E (IgE) of ≥ 76 IU/mL, and who fulfil certain criteria. In making the recommendation, the PBAC considered the rate of clinically significant asthma exacerbations and rate of severe asthma exacerbations as the primary outcomes of interest.
- 3.4 In November 2015, the PBAC recommended amendment to the PBS restriction of omalizumab 75 mg and 150 mg pre-filled syringe to allow patients with a baseline IgE 30–75 IU/mL who met all other existing PBS eligibility criteria to have the opportunity to trial omalizumab for their severe allergic asthma on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program).
- 3.5 In November 2015, the PBAC also considered and recommended the application to list omalizumab for patients with chronic spontaneous urticaria. The listing was yet to be implemented.

4 Clinical place for the proposed therapy

- 4.1 Allergic asthma is caused by allergens to which a person has been sensitised, which result in over-producing IgE antibodies directed against the allergen. Subsequent exposure to the allergen, after sensitisation, elicits an allergic response, release of inflammatory mediators, leading to symptoms such as airway narrowing, chest tightness, coughing and wheezing.
- 4.2 Omalizumab, administered as a subcutaneous injection, is an add-on treatment for the management of severe allergic asthma for patients who are treated with maximal recommended asthma maintenance medication, yet remain symptomatic. Omalizumab will be a last-line therapy.
- 4.3 The PBAC noted there is a clinical need for omalizumab. The PBAC considered that omalizumab would be beneficial to the small paediatric population that would use the proposed therapy because there are currently limited options available to treat severe allergic asthma in this group and that long term oral steroid use is unfavourable.

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

5 Comparator

- 5.1 The comparator was placebo plus optimised asthma therapy. This was an appropriate comparator.

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. At the hearing, the clinician estimated that approximately 100 children will be eligible for omalizumab in the proposed age group, confirmed the dose regime stated in the product information is used in practice and noted the anaphylaxis risks involved with subcutaneous injections. The PBAC noted the patient numbers presented were consistent with the estimates in the submission and considered that the hearing was informative as it provided a clinical perspective on treating severe asthma in the proposed population group.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with omalizumab including improved asthma control and quality of life, reduced days missed from school, reduced short-acting bronchodilator use, significantly reduced asthma exacerbation rates, clinical benefits as a result of reduced oral corticosteroid use, reduced daily inhaled corticosteroid dosage and subsequent side-effects and decreased healthcare utilisation, hospital and outpatient services.

Clinical trials

- 6.3 The submission was based on one head-to-head randomised control trial comparing omalizumab plus optimised asthma therapy to placebo plus optimised asthma therapy (n = 628) and six supplementary before/after studies. Within the key trial (IA05), the modified intention-to-treat (mITT) and one pre-specified subgroup analysis (IA05-EU) were presented. The IA05-EU subgroup included patients who were treated at baseline with inhaled corticosteroids (ICS) greater or equal to 500 µg fluticasone and a long acting beta-2 agonist (LABA). This subgroup reflected most closely the proposed PBS restriction.
- 6.4 Additionally, three ad hoc subgroups of the IA05-EU subgroup were presented in the submission (IA05-EU Responder; IA05-EU ≥3 Exacerbations; and IA05-EU ≥3 Exacerbations and Responder). The IA05-EU ≥3 Exacerbations subgroup analysis was not relevant due to the population having more severe disease than the proposed PBS restriction population. The other two ad hoc subgroup analysis, IA05-EU Responder and IA05-EU ≥3 Exacerbations & Responder, relied on the global evaluation of treatment effectiveness (GETE) tool to measure responders. There were a number of issues with these two ad hoc analyses groups:
- The placebo arm contained both responders and non-responders (measured by the GETE tool), while the treatment arm only consisted of responders. This was a biased comparison; and
 - The use of the GETE tool as a proxy for patient response might be unreasonable. When considering omalizumab for adolescents/adults in November 2009, the PBAC commented:
“The results of the meta-analysis suggest there is no statistically significant difference between treatment with omalizumab + OAT and OAT alone in investigator GETE assessment of response [RR █████, 95% CI █████].” (Paragraph 5.7.23, November 2009 PBAC Minutes); and

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“The ESC considered that the use of dichotomised GETE scores is not supported in the literature and introduced additional uncertainty in the economic evaluation. The PBAC noted while the proportion of responders and non-responders appears to favour treatment with omalizumab, no statistical analysis of the results was reported in the submission.” (Paragraph 5.7.14, November 2009 PBAC Minutes)

6.5 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
Direct randomised trial		
IA05	Novartis. A 1 year, randomized, double blind, parallel-group, placebo-controlled, multicenter evaluation of efficacy, safety, pharmacokinetics and pharmacodynamics of omalizumab in children (6 - <12 years) with moderate-severe, persistent, inadequately controlled allergic asthma. Lanier B, Bridges T, Kulus M, <i>et al.</i> Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma.	June 2008 2009 J Allergy Clin Immunol 124: 1210-1216
IA05-EU	Novartis registration document 2.7.3: Summary of Clinical Efficacy allergic asthma in children 6-<12 years of age. Kulus M, Hebert J, Garcia E, <i>et al.</i> Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma.	October 2014 2010 Curr Med Res Opin 26(6):1285-1293
Supplementary studies		
1301	Novartis. A 24 week, open label, multi-center evaluation of pharmacokinetics and pharmacodynamics, efficacy and safety of omalizumab in Japanese children (6-15 years) with inadequately controlled allergic asthma despite current recommended treatment. Odajima H, Ebisawa M, Nagakura T, <i>et al.</i> Omalizumab in Japanese children with severe allergic asthma uncontrolled with standard therapy.	Sept 2012 2015 Allergology International 64(4): 364-370
FRA-1	Deschildre A, Marguet C, Salleron J, <i>et al.</i> Add-on omalizumab in children with severe allergic asthma: a 1-year real life survey Deschildre A. Real-life long-term omalizumab therapy in children with severe allergic asthma	2013 Eur Respir J 42(5):1224-33 2015 ERJ 46(3):856-9
UK-1	Brodie M, McKean MC, Moss S, <i>et al.</i> The oral corticosteroid-sparing effect of omalizumab in children with severe asthma.	2012 Arch Dis Child 97(7):604-09
UK-2	Bossley C, Gupta A, Ullman N, <i>et al.</i> Omalizumab in children with severe asthma (SA): Which Parameters improve after a 16 week trial?	2010. Eur Resp Soc, Ann Congress (Abs P2641)
DE09	Novartis: X-HALE: (Observation of Xolair therapy under daily clinical practice Physical activity and quality of life in children and adolescents from 6 to <18 years). Kopp M, Watz H, Lerche K. Effects of Xolair in children: The X-HALE Study	2013 CSR 2013 Eur Resp Soc Conf (Abs P1133)
GER-1	Steiss JO, Strohner P, Zimmer KP <i>et al.</i> Reduction of the total IgE level by Omalizumab in children and adolescents. Steiss JO, Schmidt A, Nahrlich L <i>et al.</i> Immunoglobulin E monitoring and reduction of omalizumab therapy in children and adolescents.	2008 J Asthma 45:233-36 2012 Allergy Asthma Proc 3:77-81

Source: Table 8-10, pp47-50 of the submission

6.6 The key features of the direct randomised trial are summarised in the following table.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Main Outcome	Use in model
Key evidence						
IA05	627	R, MC, DB, PC, PG 68 weeks	Low	Moderate to severe paediatric allergic asthma	CSE rate at 24 weeks	Yes
IA05-EU ^a	235	R, MC, DB, PC, PG 68 weeks	Low	Severe paediatric allergic asthma ^b	CSE rate at 24 weeks	Yes
Supplementary evidence						
1301	38	BA, MC 24 weeks	Unclear	6-15 yrs, inadequately controlled allergic asthma	mean of serum free IgE level at 24 weeks	Yes
FRA-1	104	BA, MC 52 weeks	High	6-18 yrs, inadequately controlled allergic asthma	Effect on asthma control	Yes
UK-1	34	BA, MC 16 weeks	High	As above	Reduction in prednisolone dose from baseline	No
UK-2	20	BA 16 weeks	High	As above	NR	No
GER-1	9	BA Mean 56 months	High	As above	Change in total and free IgE	No
DE09	20	BA, MC 16–26 weeks	High	6–<18 yrs, inadequately controlled allergic asthma	PAQLQ	No

Source: compiled during the evaluation

BA = bioavailability; CSE = clinically significant exacerbation; DB = double blind; IgE = Immunoglobulin E; LABA = long acting beta-2 agonist; MC = multi-centre; NR = not reported; PAQLQ = Paediatric Asthma Quality of Life Questionnaire; PC = placebo controlled; PG = parallel group; R = randomised; yrs = years

^a This subgroup was pre-specified.

^b The population was pre-specified at baseline by criteria of inhaled corticosteroid \geq 500 μ g fluticasone and LABA user

Comparative effectiveness

- 6.7 The submission presented the clinically significant exacerbation rate at 24 and 52 weeks as the primary efficacy outcomes. Clinically significant exacerbation was defined in Study IA05 as worsening of asthma symptoms requiring doubling of the baseline ICS dose and/or treatment with rescue systemic corticosteroids for at least three days. This definition aligned closely with the proposed PBS restriction's definition of severe exacerbation, as well as with the definition in Study 2306, the main trial which supported the PBAC recommendation of omalizumab in adolescent/adults population.
- 6.8 The results for clinically significant exacerbations in the direct randomised trial are presented below.

Table 3: Clinically significant exacerbation in the direct randomised trial

Trial ID	Omalizumab + OAT		Placebo + OAT		Rate Difference	Rate ratio (95%CI)
	n	Rate	n	Rate		
Clinically significant exacerbation at 24 wks						
IA05-mITT	384	0.45	192	0.64	0.19	0.69 (0.53, 0.90)
IA05-EU ^a	159	0.42	76	0.63	0.21	0.66 (0.44, 1.00)
IA05-EU Responder ^b	118	0.33	76	0.71	0.38	0.46 (0.30, 0.72)
Clinically significant exacerbation at 52 wks						
IA05-mITT	384	0.78	192	1.36	0.58	0.57 (0.45, 0.73)
IA05-EU ^a	159	0.73	76	1.44	0.71	0.50 (0.35, 0.73)
IA05-EU Responder ^b	118	0.52	76	1.62	1.1	0.32 (0.22, 0.48)

Source: Table 24-25, pp86-87 of the submission

CI = confidence interval; GETE = global evaluation of treatment effectiveness; ICS = inhaled corticosteroids; LABA = long acting beta-2 agonist; mITT = modified intention-to-treat; n = number; OAT = optimised asthma therapy; wks = weeks; **bold** = statistically significant

^a Patients were included in this pre-specified subgroup if they were treated with LABA and were on high dose ICS

^b Of the IA05-EU subgroup, omalizumab patients were assessed as responders (rated as excellent or good on the GETE), while all placebo patients were included

- 6.9 The clinically significant exacerbation rate was significantly lower in omalizumab plus optimised asthma therapy compared with placebo plus optimised asthma therapy in each of the analysis groups. For the IA05-EU subgroup, none of the secondary outcomes were statistically significantly different between the two treatment arms (such as severe exacerbation rate, hospitalisation rate, puffs of rescue medication per day, Paediatric Asthma Quality of Life Questionnaire and lung function).
- 6.10 The supplementary before/after studies all showed a reduction in clinically significant exacerbations from before to after treatment. The reduction in clinically significant exacerbations due to omalizumab treatment was larger in the supplementary studies compared with Study IA05.

Comparative harms

- 6.11 A summary of the adverse events for omalizumab plus optimised asthma therapy and placebo plus optimised asthma therapy is presented below.

Table 4: Summary of adverse events in the IA05-mITT trial – 52 weeks

	Omalizumab + OAT N = 421	Placebo + OAT N = 207
Any adverse event	380 (90.3%)	194 (93.7%)
Mild	39.7%	36.2%
Moderate	43.0%	47.3%
Severe	7.6%	10.1%
Serious adverse event ^a	17 (4.0%)	17 (8.2%)
Withdrawals due to		
AEs	2 (0.5%)	1 (0.5%)
SAEs	1 (0.2%)	1 (0.5%)
Deaths	0	0

Source: Table 43, p102; Table 45, p103 of the submission

AE = adverse events; OAT = optimised asthma therapy; SAEs = serious adverse events

^a Does not include asthma exacerbations

- 6.12 The most commonly experienced adverse events with omalizumab therapy included nasopharyngitis (27.8% of patients), upper respiratory tract infections (16.4% of patients) and headaches (13.8% of patients).

Benefits/harms

- 6.13 A summary of the comparative benefits and harms for omalizumab plus optimised asthma therapy versus placebo plus optimised asthma therapy is presented in the table below.

Table 5: Summary of comparative benefits and harms for Omalizumab + OAT and Placebo + OAT

Trial	Omalizumab + OAT	Placebo + OAT	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Omalizumab + OAT	Placebo + OAT	
Benefits						
Rate of clinically significant exacerbations at 52 weeks						
IA05-EU Responder ^a	0.52	1.62	0.32 (0.22, 0.48)	52	162	-1.10
IA05-EU ^b	0.73	1.44	0.50 (0.35, 0.73)	73	144	-0.71
Harms						
	Omalizumab + OAT	Placebo + OAT	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Omalizumab + OAT	Placebo + OAT	
Nasopharyngitis						
IA05-mITT	117/421	56/207	1.03 (0.78, 1.35)	27.8	27.1	0.01 (-0.07, 0.09)
Upper respiratory tract infection						
IA05-mITT	69/421	46/207	0.74 (0.53, 1.03)	16.4	22.2	-0.06 (-0.13, 0.01)
Headache						
IA05-mITT	58/421	33/207	0.87 (0.04, 1.29)	13.8	15.9	-0.02 (-0.08, 0.04)

Source: Table 25, p87; Tables 41-42, pp100-101; Table 44, p102 of the submission

CI = confidence interval; ICS = inhaled corticosteroids; LABA = long acting beta-2 agonist; mITT = modified intention-to-treat; OAT = optimised asthma therapy; RD = risk difference; RR = rate ratio

* Median duration of follow-up: IA05-mITT = 52 weeks

^a Of the IA05-EU subgroup, omalizumab patients were assessed as responders (rated as excellent or good on the GETE), while all placebo patients were included

^b Patients were included in this prespecified subgroup if they were treated with LABA and were on high-dose ICS

- 6.14 On the basis of direct comparison evidence presented by the submission, for every 100 patients treated with omalizumab plus optimised asthma therapy in comparison with placebo plus optimised asthma therapy, there was a reduction of approximately 71 clinically significant exacerbations over a duration of 52 weeks.

Clinical claim

- 6.15 The submission described omalizumab as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over placebo.
- 6.16 In terms of the effectiveness claim, it was noted that the clinically significant asthma exacerbation rate was the only outcome to be significantly different to placebo in the IA05-EU subgroup, as there were no differences between omalizumab and placebo for the severe exacerbation rate, hospitalisation rate, puffs of rescue medication per

day, Paediatric Asthma Quality of Life Questionnaire, and lung function (forced expired volume in one second, and forced vital capacity).

- 6.17 The following limitations were noted with the claim of non-inferior safety:
- Only limited safety data were available; and
 - For the adolescent/adult population (November 2010), there was a potentially higher incidence of cardiovascular and cerebrovascular events in patients using omalizumab was raised with the TGA and FDA by the sponsor. Thus, it could not be concluded that omalizumab was as safe as placebo when added to optimised asthma therapy. Therefore, the PBAC considered that omalizumab was inferior to placebo in terms of safety (Paragraph 7.2.12, November 2010 PBAC Minutes). Although omalizumab had been licenced for use in children in the UK and the EU, paediatric use had not been supported in Canada or the US due to concerns about effectiveness and safety. Specifically, the ESC noted that in 2011 an FDA review made the following conclusion for paediatric patients 6 to less than 12 years, based on the IO05 RCT used in this submission to PBAC:
“Due to the risk of anaphylaxis and malignancy seen in adult and adolescent patients treated with Xolair and the modest efficacy of Xolair® seen in the randomized controlled trial in 6 to < 12 years patients, the risk-benefit assessment does not support the use of Xolair® in this age group.”
- 6.18 The PSCR (p6) noted that in July 2015 the sponsor received written FDA feedback stating that additional safety data had become available that lowers the risk and creates a more favourable risk/benefit relationship for the paediatric population. The PSCR confirmed that resubmission applications will be in the US and Canada and that these will be based on the same study (Study IA05) as the current submission to the PBAC.
- 6.19 The pre-PBAC response (p2) included an article from the New England Journal of Medicine which was submitted as additional safety data to the US and Canada. The PBAC considered the ICATA¹ study as supportive evidence and noted that despite the slightly different age group of the study population (ages 6-20 years) to the proposed population, the data demonstrated that omalizumab was more effective when compared to placebo.
- 6.20 The PBAC noted that the pre-PBAC response (p2) addressed concerns in relation to arterial thromboembolic events which is included as a potential risk in the summary of ongoing safety concerns in the TGA-approved risk management plan.
- 6.21 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.22 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

¹ Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011; 364:1005-15.

Economic analysis

6.23 The submission presented a trial-based economic evaluation, based on the direct randomised trial, Study IA05 and its subgroups, and performed a responder analysis using the clinically significant exacerbation rate as the outcome. The type of economic evaluation presented was a cost-effectiveness analysis in the form of cost per clinically significant exacerbation avoided.

Table 6: Summary of model structure and rationale

Component	Summary
Time horizon	One year in the model base case, based on 52 weeks in the trial
Outcomes	Rate of clinically significant exacerbations per year
Methods used to generate results	Cost of omalizumab – cost of placebo / omalizumab CSE rate – placebo CSE rate.
Discount rate	No discount rate was used due to one year time horizon.
Software package	Excel 2010

Source: compiled during the evaluation
CSE = clinically significant exacerbation

6.24 The key driver of the cost-effectiveness model was the difference between omalizumab and placebo exacerbation rates.

Table 7: Key drivers of the model

Description	Method/Value	Impact
Exacerbation rate difference	Difference between omalizumab and placebo exacerbation rates	High (low if IA05-EU pre-specified sub-group selected) (favoured omalizumab)

Source: compiled during the evaluation

6.25 The cost per exacerbation included hospitalisation costs, which might be overestimated. The submission estimated a non-validated weighted cost across AR-DRGs E41A/B (respiratory system disorders with non-invasive ventilation), E62A/B/C (respiratory infections/inflammations), E67A/B (respiratory signs and symptoms) and E69A/B (bronchitis and asthma). The cost per separation for E41A/B was substantially higher than for E69A/B (\$█████-\$█████ versus \$█████-\$█████, respectively). Using only AR-DRG E69A and E69B costs reduces the estimated exacerbation treatment cost from \$█████ to \$█████.

6.26 The PSCR (p3-4) argued that patients were likely to be admitted under E62 respiratory infections/inflammation and recalculated the weighted DRG excluding the highest cost DRG E41 respiratory disorders with non-invasive ventilation. The new weighted cost per admission was \$█████, and the updated ICERs presented in the PSCR were based on the updated DRG figures.

- 6.27 The results of the economic model are presented in the table below. These results were updated from the original submission to account for the updated effective price as well as the updated cost per exacerbation calculated by the PSCR.

Table 8: Results of the economic evaluation – updated effective omalizumab price (1 June 2016) and cost per exacerbation (\$████)

	Omalizumab + OAT	Placebo + OAT	Increment
IA05-EU Responder^a			
Costs	\$████	\$████	\$████
CSE	0.52	1.62	-1.10
Incremental cost/extra CSE avoided			\$████
IA05-EU^b			
Costs	\$████	\$████	\$████
CSE	0.73	1.44	-0.71
Incremental cost/extra CSE avoided			\$████
IA05-mITT			
Costs	\$████	\$████	\$████
CSE	0.78	1.36	-0.58
Incremental cost/extra CSE avoided			\$████
IA05-EU continuation rule – Proposed new base case in PSCR			
Costs	\$████	\$████	\$████
CSE	0.64	1.44	-0.80
Incremental cost/extra CSE avoided			\$████
IA05-EU continuation rule^c – Proposed new base case – using methodology of commentary			
Costs	\$████	\$████	\$████
CSE	0.77	1.44	-0.67
Incremental cost/extra CSE avoided			\$████

Source: Economic model spreadsheet provided with the PSCR

CSE = clinically significant exacerbation; GETE = global evaluation of treatment effectiveness; ICS = inhaled corticosteroids; LABA = long acting beta-2 agonist; mITT = modified intention-to-treat; OAT = optimised asthma therapy; PSCR = Pre-Sub Committee Response

^a In the IA05-EU subgroup, omalizumab patients were assessed as responders (rated as excellent or good on the GETE), while all placebo patients were included

^b Patients were included in this pre-specified subgroup if they were treated with LABA and were on high dose ICS

^c The estimated exacerbation rate for omalizumab was 0.77, and 24% would be non-responders receiving 24 weeks of treatment only.

- 6.28 The redacted table shows that the proposed new base case and the proposed new base case using methodology of commentary are both less than \$15,000 per clinically significant exacerbation avoided..
- 6.29 The submission estimated a cost per clinically significant exacerbation avoided of \$████ in the IA05-EU Responder subgroup, which according to the submission best reflected the proposed PBS population. The ESC agreed with the commentary that the subgroup used in the base case was inappropriate due to the exclusion of non-responders in the omalizumab arm, while all patients were included in the placebo arm. These non-responders in the omalizumab arm would be treated for 24 weeks, and therefore costs and clinically significant exacerbations would be accrued. Therefore, the most appropriate analysis group of those presented by the submission was the IA05-EU subgroup, in which the ICER was estimated to be less than \$15,000 per clinically significant exacerbation avoided.

- 6.30 The PSCR (p4) applied the continuation criteria to the IA05-EU subgroup to give a more appropriate base case population. In this case the ICER was estimated to be less than \$15,000 per clinically significant exacerbation avoided.
- 6.31 The submission did not provide sensitivity analyses. During the evaluation, sensitivity analyses were performed, using: a shorter time frame; the adolescent/adult populations (using Studies 2306 and 2425, which formed the basis for the PBAC’s November 2010 recommendation in this population); and severe clinically significant exacerbations as an outcome. The results of these sensitivity analyses (using the updated prices provided in the PSCR) are presented in the table below.

Table 9: Results of the sensitivity analyses –conducted during evaluation – updated effective omalizumab price (1 June 2016)

	Δ Cost	Δ CSE	ICER (cost/CSE avoided)
Clinically significant exacerbations (\$ [redacted])			
Paediatric population			
IA05-EU – 52 weeks	\$ [redacted]	-0.71	\$ [redacted]
IA05-EU – 24 weeks	\$ [redacted]	-0.21	\$ [redacted]
Adolescent/adult population ^a			
2306 – 28 weeks	\$ [redacted]	-0.22	\$ [redacted]
2425 – 32 weeks	\$ [redacted]	-0.43	\$ [redacted]
Severe clinically significant exacerbation (cost per severe exacerbation = \$ [redacted])			
Paediatric population			
IA05-EU – 52 weeks	\$ [redacted]	-0.22	\$ [redacted]
IA05-EU – 24 weeks	\$ [redacted]	-0.08	\$ [redacted]
Adolescent/adult population ^a			
2306 – 28 weeks	\$ [redacted]	-0.24	\$ [redacted]
2425 – 32 weeks	\$ [redacted]	-0.18	\$ [redacted]

Source: Table 76, p181 of the submission; and constructed during the evaluation

CSE = clinically significant exacerbation; ICER = incremental cost effectiveness ratio; PBS = Pharmaceutical Benefits Scheme

^a The dosing for adults was sourced from tab “ChildvsAdolAd” in the section D workbook of the submission

The redacted table shows ICERs in the range of less than \$15,000 per CSE avoided, \$15,000 - \$45,000/CSE avoided and \$45,000- \$75,000/CSE avoided.

- 6.32 The sensitivity analyses showed:
- The cost per clinically significant exacerbation avoided was reasonably similar between the paediatric and adolescent/adult population; and
 - The cost per severe exacerbation avoided was higher in the paediatric population compared with the adolescent/adult population.
- 6.33 The ESC acknowledged the difficulties inherent in determining utility values to inform a cost-utility analysis in the proposed population, noting in particular that it is difficult to estimate utilities in paediatric populations, but considered that it was difficult to interpret the cost per clinically significant exacerbation avoided. Overall the ESC considered that:
- The comparison of cost per clinically significant exacerbation avoided in the paediatric population compared to the adolescent/adult population suggested similar cost-effectiveness based on this outcome, but the cost per severe exacerbation avoided is higher in the paediatric population;
 - It is difficult to directly interpret the cost per clinically significant exacerbation avoided in a QALY framework because the impact of exacerbations on mortality

and quality of life has not been modelled, though health care costs (including hospitalisations) associated with exacerbations are included in the reported ICERs; and

- To provide a frame of reference for interpreting a cost per clinically significant exacerbation in a QALY framework, the ESC noted that if no mortality effect is modelled, an exacerbation would need to be lead to a loss of 0.28 QALYs to achieve an ICER of \$50,000 per QALY.

Drug cost/patient/year: \$ [REDACTED]

6.34 The drug cost/patient/year for omalizumab is based on the effective price of \$ [REDACTED] per patient per four weeks. This was based on the IA05-EU dosing schedule where on average 0.6 x 75 mg syringes and 2.2 x 150 mg syringes were used every four weeks, and included the [REDACTED] % rebate. This four-weekly cost was multiplied by 13 to get the yearly cost per patient of \$ [REDACTED].

Estimated PBS usage and financial implications

This submission was not considered by DUSC.

6.35 The submission presented an epidemiological approach to the analysis of the financial impact of listing omalizumab on the PBS. The submission modified the approach that it took for the listing of omalizumab for the adult population (November 2010). The PSCR (p6) provided the following table of financial implications updated to account for the change in SPA.

Table 10: Estimated use and financial implications – updated effective omalizumab price (1 June 2016)

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated (responders)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Market share	50%	50%	50%	50%	50%
Scripts ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source Table 2, p6 of the Pre Sub-Committee Response

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Assuming 16.9 scripts per year for responders and 9.1 scripts for non-responders as estimated by the submission.

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

6.36 The estimated financial implications for the PBS/MBS of listing omalizumab might be an under- or overestimate given:

- the possible underestimation of the number of patients likely to be eligible for treatment with omalizumab due to multiple measures of disease severity with unknown overlaps in populations being applied sequentially; and
- the unknown uptake rate.

- 6.37 In the pre-PBAC response (p4) it was stated that omalizumab is currently underutilised compared with the estimates (DUSC PRD 2014). The PBAC agreed with the estimates, considered that there was a low risk of leakage due to the drug's various clinical implications such as subcutaneous administration and potential anaphylaxis risks, and would therefore only be used when necessary. The PBAC questioned the reduction in responders presented in the estimate of utilisation, however, given the change was minimal, the PBAC considered it acceptable.

Financial Management – Special Pricing Arrangement

- 6.38 The PSCR (p1) reported that the SPA had been updated since the time of submission.
- 6.39 Under the new SPA, effective 1 June 16, the rebate was ██████%. The effective prices were \$██████ for 75 mg and \$██████ for 150 mg.

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

7 PBAC Outcome

- 7.1 The PBAC recommended a written Authority Required Section 100 (Highly Specialised Drugs Program) listing of omalizumab for treatment of severe allergic asthma in patients aged 6 to less than 12 years. The PBAC was satisfied that omalizumab provides, for some patients, a significant improvement in efficacy over placebo plus optimised asthma therapy.
- 7.2 The PBAC recommended that the restriction for the proposed age group be as consistent as possible with the adult population given the results from the clinical trials were similar in the paediatric and adult groups. The PBAC noted the suggestion that the threshold for exacerbations be increased, but considered that increasing the threshold from two to three was immaterial and recommended the restriction remain as two exacerbations as proposed.
- 7.3 The PBAC agreed there was a clinical place for the proposed therapy and noted that there are currently limited options available to treat the proposed group and that long-term oral steroid use is unfavourable. Additionally, the PBAC considered that there was a low risk of leakage due to the drug's various clinical implications such as subcutaneous administration and potential anaphylaxis risks and would therefore only be used when necessary.
- 7.4 The PBAC agreed that placebo plus optimised asthma therapy was the appropriate comparator.
- 7.5 The PBAC noted the limitations of the clinical trial data presented, but considered that there was no biologically plausible reason for effect modification based upon age. The PBAC considered clinical trial evidence that demonstrated that there were similar outcomes in the paediatric population when compared to the adult population.
- 7.6 The PBAC noted the clinically significant exacerbation rate was significantly lower in omalizumab plus optimised asthma therapy compared with placebo plus optimised

asthma therapy in each of the analysis groups. For the IA05-EU subgroup, none of the secondary outcomes were statistically significantly different between the two treatment arms (such as severe exacerbation rate, hospitalisation rate, puffs of rescue medication per day, Paediatric Asthma Quality of Life Questionnaire and lung function). The PBAC considered that this was acceptable as the ICATA study demonstrated there were benefits in a paediatric population being treated with omalizumab.

- 7.7 Similarly, the PBAC noted there were some limitations to the safety data, but considered the additional data that were lodged to the US and Canada for the assessment of paediatric safety addressed these concerns.
- 7.8 The PBAC considered the economic model to be reasonable where a cost effectiveness analysis was presented in the form of cost per clinically significant exacerbation avoided. The economic model was based on the direct randomised trial, Study IA05 and its subgroups and performed as a responder analysis using the clinically significant exacerbation rate as the outcome. Additionally, the claim of cost-effectiveness was supported by the PBAC's previous consideration that omalizumab treatment was cost-effective in the adolescent and adult populations.
- 7.9 The PBAC noted that the total number of patients utilising the drug would be low and therefore considered the total cost of the drug to be relatively low. The clinician in the sponsor hearing confirmed the utilisation of omalizumab in the proposed population. The PBAC questioned the reduction in responders in the estimate of utilisation. However, PBAC noted that it was acceptable in this case as the change was minimal.
- 7.10 The PBAC recommended that omalizumab should not be treated as interchangeable with any other drugs.
- 7.11 The PBAC advised that Section 100 medicines are currently considered out of scope for prescribing by nurse practitioners.
- 7.12 The PBAC noted that the Early Supply Rule does not currently apply to Section 100 listings, but should this change in the future the Committee considered that it would be appropriate for the Early Supply Rule to apply to omalizumab.
- 7.13 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing/recommended listing as follows:

To be finalised

9 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.

10 Sponsor's Comment

Novartis is very pleased that children with severe allergic asthma will have access to omalizumab via the PBS. Novartis wishes to thank the consumer organisations and physicians that supported this submission, as well as the PBAC and government.