

5.05 MEPOLIZUMAB, lyophilised powder for subcutaneous injection, 100 mg, Nucala®, GlaxoSmithKline.

1 Purpose of Application

- 1.1 The submission requested a Section 100 (Highly Specialised Drug (HSD) Program) listing for mepolizumab for treatment of severe eosinophilic asthma in patients aged 12 years and over.

2 Requested listing

- 2.1 Proposed PBS listing (abridged):

Name, restriction, manner of administration and form	Max Qty	No. of Rpts	Ex-manufacturer price	Proprietary name and manufacturer	
MEPOLIZUMAB 100 mg lyophilised powder in a single-use vial for subcutaneous injection	1	0	\$ [REDACTED]	Nucala®	GlaxoSmithKline
Treatment phase	Initial treatment				
Restriction	Section 100 HSD				
Clinical criteria	<p>Patient must be under the same care of the same physician for at least 12 months; AND Patient must have a diagnosis of asthma confirmed and documented by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma, defined by the following standard clinical features:</p> <ul style="list-style-type: none"> (i) FEV₁ reversibility greater than or equal to 12% and greater than or equal to 200 mL at baseline within 30 minutes after administration of salbutamol (200 to 400 µg), or (ii) airway hyper-responsiveness defined as a greater than 20% decline in FEV₁ during a direct bronchial provocation test or greater than 15% decline during an indirect bronchial provocation test, or (iii) PEF variability of greater than 15% between the two highest and two lowest peak expiratory flow rates during 14 days; AND <p>Patient must have a duration of asthma of at least 1 year; AND Patient must have forced expiratory volume (FEV₁) less than or equal to 80% predicted, documented on 1 or more occasions in the previous 12 months; AND Patient must have blood eosinophil count ≥ 300 cells µL in the last 6 weeks; AND Patient must have signed a patient acknowledgement indicating they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criteria for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment; AND Patient must have failed to achieve adequate control with optimised asthma therapy, despite formal assessment of and adherence to correct inhaler technique, which has been documented; AND Patient must not receive more than 32 weeks of treatment under this restriction.</p>				
Population criteria	Patient must be aged 12 years or older				
Treatment criteria	Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.				

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Name, restriction, manner of administration and form	Max Qty	No. of Rpts	Ex-manufacturer price	Proprietary name and manufacturer	
MEPOLIZUMAB 100 mg lyophilised powder in a single-use vial for subcutaneous injection	1	0	\$ [REDACTED]	Nucala®	GlaxoSmithKline
Treatment phase	Continuing treatment				
Restriction	Section 100 HSD				
Clinical criteria	Patient must have a documented history of severe eosinophilic asthma; AND Patient must have demonstrated or sustained an adequate response to treatment with this drug; AND Patient must not receive more than 32 weeks of treatment under this restriction.				
Treatment criteria	Must be treated by a respiratory physician, clinical immunologist, allergist or general physician experienced in the management of patients with severe asthma.				

2.2 In addition, the sponsor wished to work with the PBAC to agree on a separate grandfathering restriction for patients currently enrolled in clinical trials. It further proposed that a balance of supply restriction, similar to omalizumab, be drafted post positive recommendation, to account for patients who have received insufficient therapy under the initial treatment restriction to complete a 32-week treatment cycle.

2.3 The submission presented:

- A cost-effectiveness analysis of mepolizumab with standard of care as the main comparator for those patients not eligible for omalizumab but eligible for mepolizumab; and
- A cost-minimisation analysis of mepolizumab with omalizumab as the main comparator for patients eligible for both mepolizumab and omalizumab.

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

3 Background

3.1 The submission was made under TGA/PBAC Parallel Process. Mepolizumab was approved for registration in the Australian Register of Therapeutic Goods (ARTG), as an add-on treatment for severe refractory eosinophilic asthma in patients aged 12 years and over, on 25 January 2016. At the time of evaluation, the Clinical Evaluation Report and Delegate Overview were available.

3.2 Mepolizumab has not previously been considered by the PBAC.

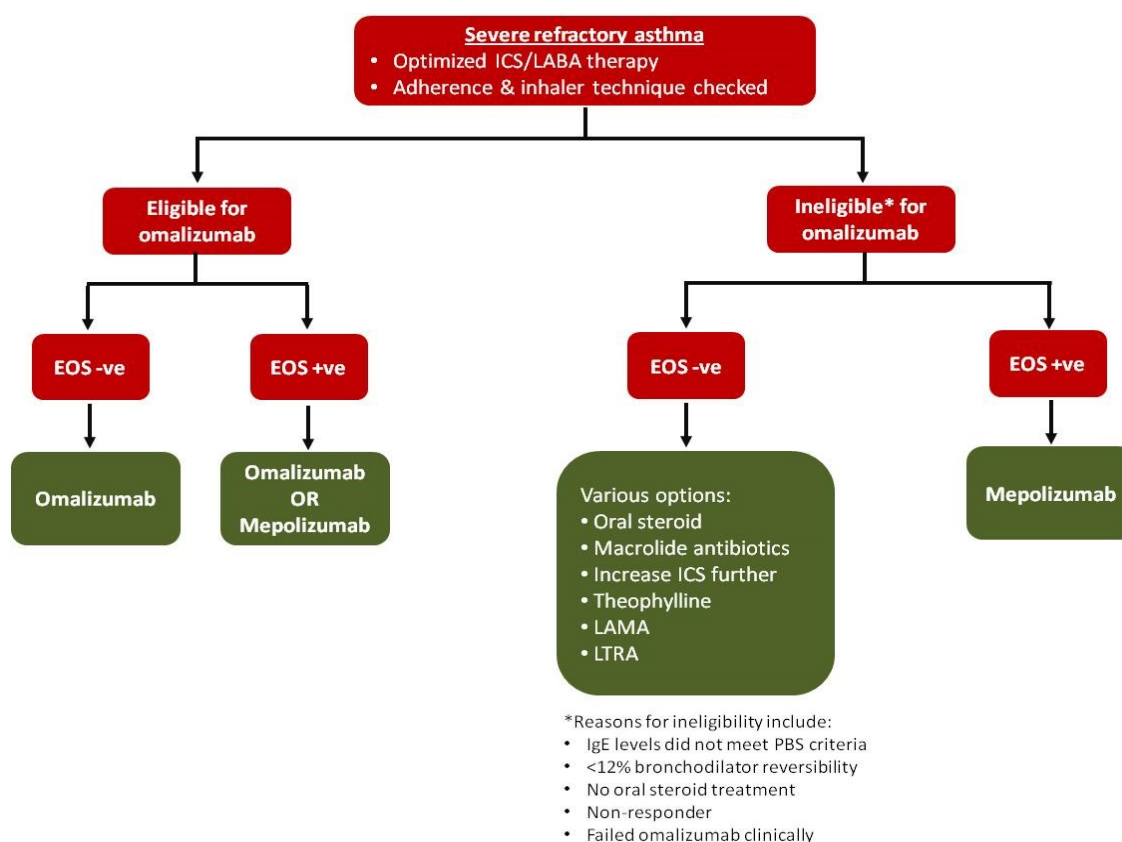
3.3 Omalizumab is a monoclonal antibody that targets immunoglobulin E (IgE) and was listed on the PBS in 2011 for severe asthma with evidence of an IgE phenotype. It is the only monoclonal antibody currently listed on the PBS for the treatment of severe refractory asthma. While mepolizumab targets the interleukin-5 pathway (i.e. eosinophil-mediated inflammation), omalizumab more broadly targets IgE asthma meaning there will be overlap between the eligible populations when both pathways are operating. Mepolizumab and omalizumab are not intended to be given concurrently.

- 3.4 At the November 2015 meeting the PBAC recommended expanding the listing of omalizumab for the treatment of severe allergic asthma in patients with a baseline IgE of 30-75 IU/mL on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program).
- 3.5 At the March 2016 meeting, the PBAC is also considering tiotropium, a Long-Acting Muscarinic Antagonist (LAMA) for the treatment of severe asthma in adults who have experienced at least one severe exacerbation, which has required use of systemic corticosteroids, in the previous 12 months while receiving optimised asthma therapy.

4 Clinical place for the proposed therapy

- 4.1 Eosinophilic asthma is a Type 2 T helper driven asthma inflammation which differs from atopic and allergic asthma in that it is usually later-onset (≥ 20 years), more severe, less allergic and is often refractory to corticosteroid therapy. Patients suffer from persistent symptoms and acute exacerbations despite treatment with high-dose inhaled corticosteroids (ICS) plus additional controller therapy. Some patients who have eosinophilic asthma also have allergic asthma.
- 4.2 Mepolizumab is recommended as an add-on therapy for patients with eosinophilic severe asthma. Mepolizumab would be used in combination with standard of care. It is given by subcutaneous (SC) injection once every four weeks.
- 4.3 As shown in the figure below, in patients with eosinophilic asthma who are eligible for omalizumab, mepolizumab provides an additional treatment option. In patients with eosinophilic asthma who aren't eligible for omalizumab mepolizumab will provide an alternative to standard medical management.

Figure 1: Severe asthma treatment pathway



Source: Attachment A2 of the submission, p.13 mepolizumab advisory board minutes

- 4.4 The PBAC received advice from the Thoracic Society of Australia and New Zealand (TSANZ) regarding the clinical distinction between eosinophilic asthma and IgE driven asthma. The PBAC noted the advice that eosinophilic asthma and IgE driven asthma are two distinct phenotypes with different molecular pathways and targeted therapies, and that while there is some overlap between the two asthma phenotypes, there is sufficient distinction to allow recognition and application of different therapies to each phenotype.

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

5 Comparator

- 5.1 The proposed PBS population for mepolizumab includes two distinct groups of patients with eosinophilic asthma: those currently eligible for omalizumab (in whom mepolizumab will replace omalizumab) and those who are ineligible for omalizumab (in whom mepolizumab adds an additional option to standard medical management). For this reason, the submission nominated two comparators:

1. Placebo/standard of care in patients not currently eligible for omalizumab.
2. Omalizumab in patients who are currently eligible for omalizumab.

The comparators were appropriate.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a need for new targeted drugs to treat eosinophilic asthma and the potential for mepolizumab to improve quality of life for patients. The comment from the National Asthma Council Australia highlighted that for patients with severe asthma and difficult to control symptoms, there are costs to the community in terms of lost productivity, more hospitalisations, formal care costs and reduced quality of life.

Clinical trials

6.3 The submission presented a direct comparison (against standard of care) and an indirect comparison (against omalizumab). The direct comparison was based on three head-to-head trials comparing mepolizumab to standard of care (Studies 588, 575 and 997). The indirect comparison was based on six head-to-head trials; two comparing mepolizumab to standard of care (Studies 588 and 997) and four comparing omalizumab to standard of care (INNOVATE, EXTRA, ETOPA and EXALT).

6.4 Details of the trials presented in the submission are provided in the table below. While the submission presented details for the ETOPA study, no relevant efficacy or safety results were presented.

Table 1: Trials and associated reports presented in the submission

Trial	Protocol title/Publication title	Publication citation
Direct randomised trials		
Mepolizumab versus standard of care		
Study 588	MEA115575: A randomized, double-blind, double-dummy, standard of care-controlled, parallel-group, multi-centre study of the efficacy and safety of mepolizumab adjunctive therapy in subjects with severe uncontrolled refractory asthma. Ortega HG, Liu MC, Pavord ID, <i>et al.</i> Mepolizumab treatment in patients with severe eosinophilic asthma.	10 June 2010 <i>NEJM.</i> 2014; 371 (13): 1198-1207.
Study 575	MEA115575: A randomized, double-blind, placebo-controlled, parallel group, multicentre study of mepolizumab adjunctive therapy to reduce steroid use in subjects with severe refractory asthma. Bel EH, Wenzel SE, Thompson PJ, <i>et al.</i> Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma.	22 May 2014 <i>NEJM.</i> 2014; 371(13): 1189-1197.

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Trial	Protocol title/Publication title	Publication citation
Study 997	<p>A multicentre, randomised, double-blind, standard of care-controlled, parallel group, dose ranging study to determine the effect of mepolizumab on exacerbations rates in subjects with severe uncontrolled refractory asthma.</p> <p>Pavord ID, Kom S, Howarth P, <i>et al.</i> Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, standard of care-controlled trial.</p>	<p>20 September 2014</p> <p><i>Lancet.</i> 2012; 380(9842): 651-659.</p>
Omalizumab versus standard of care		
INNOVATE	<p>Humbert M, Beasley R, Ayres J, <i>et al.</i> Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE.</p> <p>Humbert M, Berger SW, Rapatz G, <i>et al.</i> Add-on omalizumab improves day-to-day symptoms in inadequately controlled severe persistent allergic asthma.</p> <p>Stoeger ZM, Eliraz A, Asher I, <i>et al.</i> The beneficial effects of Xolair® (omalizumab) as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available treatment (GINA 2002 step IV) – the Israeli arm of the INNOVATE study.</p>	<p><i>Allergy.</i> 2005; 60(3): 309-316.</p> <p><i>Allergy.</i> 2008; 63(5): 592-596.</p> <p><i>J Allergy Clin Immunol.</i> 2007; 9: 472-475.</p>
EXTRA	<p>Hanania NA, Alpan O, Hamilos DL, <i>et al.</i> Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial.</p> <p>Hanania NA, Wnzel S, Rosen K, <i>et al.</i> Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study.</p>	<p><i>Ann Intern Med.</i> 2011; 154(9): 573-582.</p> <p><i>Am J Respir Crit Care Med.</i> 2013; 187(8): 804-844.</p>
ETOPA	<p>Niven R, Chung KF, Panahloo Z, <i>et al.</i> Effectiveness of omalizumab in patients with inadequately controlled severe persistent allergic asthma: and open-label study.</p> <p>Ayres JG, Higgins B, Chilvers ER, <i>et al.</i> Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate to severe) allergic asthma.</p>	<p><i>Respir Med.</i> 2008; 102(10): 1371-1378.</p> <p><i>Allergy.</i> 2004; 59(7): 701-708.</p>
EXALT	<p>Bousquet J, Siergiejko Z, Swiebocka E, <i>et al.</i> Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma patients.</p> <p>Siergiejko Z, Swiebocka E, Smith N, <i>et al.</i> Oral corticosteroid sparing with omalizumab in severe allergic (IgE-mediated) asthma patients.</p>	<p><i>Allergy.</i> 2011; 66(5): 671-678</p> <p><i>CMRO.</i> 2011; 27(11): 2223-2228.</p>

Source: Table 15, pp56-57; Tables 55-56, pp157-159 of the submission

IgE = immunoglobulin E

6.5 The key features of the direct randomised trials are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Mepolizumab versus standard of care						
Study 575	135	R, DB, MC 24 weeks	Low	Severe, eosinophilic asthma	Reduction in OCS dose	No
Study 588	580	R, DB, MC 32 weeks	Low	Severe, uncontrolled, refractory asthma	Rate of exacerbations	Yes, subgroup - CEA, CMA
Study 997	311	R, DB, MC 52 weeks	Low	Severe, uncontrolled, refractory asthma	Rate of exacerbations	No
Omalizumab versus standard of care						
INNOVATE	482	R, DB, MC 32 weeks	Unclear	Severe, persistent, allergic asthma	Rate of exacerbations	Yes - CMA
EXALT	408	R, OL, MC 32 weeks	High	Severe, uncontrolled, allergic asthma	Persistency rate of response	No
EXTRA	850	R, DB, MC 48 weeks	Low	Severe, uncontrolled, allergic asthma	Rate of exacerbations	No

Source: *Compiled during the evaluation*

CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; DB = double blind; MC = multi-centre; OCS = oral corticosteroid; OL = open label; R = randomised

- 6.6 The patient populations used in the direct and indirect comparisons and in the economic evaluations and how they compare to the (proposed) PBS restrictions are presented below.

Table 3: Populations used in the direct and indirect comparisons presented in the submission

	Eosinophils (cells/ μ L)			Exac	Min IgE (IU/mL)	+ve RAST	Econ model
	≥ 150 in last 6 wks	≥ 300 in last 6 wks	≥ 300 in last 12 mths				
PBS Restrictions							
Mepolizumab		Y		≥ 1			
Omalizumab				≥ 1	76	Y	
Direct comparison (mepolizumab versus SOC)							
Study 588: ITT population	Y		Y	≥ 2			-
Subgroup	-	Y	-	≥ 2			CEA
Study 575: ITT population	Y		Y				
Study 997: Subgroup	Y		Y	≥ 2			
Indirect comparison (mepolizumab versus omalizumab)							
Mepolizumab: Study 588, 100 mg SC ITT population	Y		Y	≥ 2	-	-	-
1° analysis	Y		Y	≥ 2	30	Y	CMA
2° analysis	Y		Y	≥ 2	30	Y	-
Omalizumab: ITT population (INNOVATE + EXTRA)				≥ 1	30	Y	-
1° analysis (INNOVATE + EXTRA)				≥ 1	30	Y	-
2° analysis (INNOVATE)				≥ 2	30	Y	CMA

Source: *Compiled during evaluation*

CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; Econ = economic; Exac = exacerbations; IgE = immunoglobulin E; ITT = intention-to-treat; Min = minimum; PBS = Pharmaceutical Benefits Scheme; RAST = radioallergosorbent test; SC = subcutaneous; SOC = standard of care; wks = weeks; Y = yes; +ve = positive; 1° = primary; 2° = secondary; **Bold** = data used in the key analyses

- 6.7 For the direct comparison between mepolizumab and standard of care the submission relied on a subgroup analysis from Study 588. Patients matched the

proposed PBS restriction in terms of eosinophil count but had experienced at least two exacerbations in the last twelve months, rather than one.

- 6.8 For the indirect comparison between mepolizumab and omalizumab the submission relied on a subgroup analysis from Study 588 and intention-to-treat (ITT) population analyses for omalizumab. The populations included in the indirect comparison did not precisely match the proposed mepolizumab and current omalizumab PBS restrictions. The key differences were lower serum IgE levels (≥ 30 IU/mL) in the trials compared to the omalizumab PBS restriction (≥ 76 IU/mL), no limits on eosinophil levels in the omalizumab trials, and patients needed to have at least two exacerbations in the last twelve months.
- 6.9 The key outcome was the rate of exacerbations. The definitions and time periods for this outcome are presented below.

Table 4: Definitions of clinically significant exacerbations and exacerbation rate time periods as per the individual trials used in the submission

Trial	Definition of clinically significant exacerbation	Time period for exacerbation rate
Mepolizumab trials		
Study 575	Systemic corticosteroids \pm hospitalisation \pm ED visits ^a	Rate per year
Study 588	Systemic corticosteroids \pm hospitalisation \pm ED visits ^a	Rate per year
Study 997	Oral/systemic corticosteroids \pm hospitalisation \pm ED visits ^a	Rate per year
Omalizumab trials used for the indirect comparison		
INNOVATE	Systemic corticosteroids.	Rate per 24 weeks
EXTRA	Systemic corticosteroids.	Rate per patient year

Source: Section 4.6.2.1, p34 of Study 588 CSR; Section 4.6.2.1, p38 of Study 997 CSR; Section 4.6.2.3, p32 of Study 575 CSR; and individual trial papers

ED = emergency department; OCS = oral corticosteroid

^a For patients receiving long-term OCS, an exacerbation was at least doubling of the existing maintenance dose for ≥ 3 days

- 6.10 The definitions for clinically significant exacerbations differed between the trials; with the use of systemic corticosteroids the only requirement in the omalizumab trials, compared to the use of systemic corticosteroids and/or hospitalisation and/or emergency department visits in the mepolizumab trials. Further, the exacerbation rates were expressed inconsistently between the trials.

Comparative effectiveness

Direct comparison of mepolizumab versus standard of care

- 6.11 The submission presented number and frequency of clinically significant exacerbations as the primary efficacy outcome. The results for the comparison with standard of care are presented below.

Table 5: Yearly rate of clinically significant exacerbations in the mepolizumab randomised trials

	MEPO 100 mg SC		MEPO 75 mg IV		SOC		RR, (95% CI)
	N	Rate/year	N	Rate/year	N	Rate/year	
Main analysis: Eosinophils of ≥ 150 cells/μL in the 6 weeks prior to screening or ≥ 300 cells/μL in the 12 months prior to screening (as per proposed TGA indication)							
Trial duration: 24-32 weeks							
Study 588 - ITT pop	194	0.83	-	-	191	1.74	0.47 (0.35, 0.64)
	-	-	191	0.93			0.53 (0.40, 0.72)
Study 575 - ITT pop	69	1.44	-	-	66	2.12	0.68 (0.47, 0.99)
Trial duration: 52 weeks							
Study 997- Subgroup	-	-	126	1.18	137	2.40	0.49 (0.35, 0.67)
Subgroup: Eosinophils of ≥ 300 cells/μL in the 6 weeks prior to screening (per proposed PBS restriction)							
Study 588 - Subgroup	100	0.71	-	-	106	1.98	0.36 (0.24, 0.54)
	-	-	102	0.85			0.43 (0.29, 0.64)

Source: Tables 32-33, pp106-107 of the submission; and Table 28, p89 of Study 997 CSR

CI = confidence interval; ITT = intention-to-treat; IV = intravenous; MEPO = mepolizumab; PBS = Pharmaceutical Benefits Scheme; pop = population; RR = rate ratio; SC = subcutaneous; SOC = standard of care; TGA = Therapeutic Goods Administration

- 6.12 The exacerbation rates were significantly lower in the mepolizumab arms of the trials compared to the standard of care arms (ITT populations and subgroup analyses).
- 6.13 The submission stated that the subgroup analysis of patients from Study 588 with a baseline eosinophil count of ≥ 300 cells/ μ L in the six weeks prior to screening confirmed that the relative efficacy of mepolizumab was increased. Baseline characteristics for this subgroup were not provided in the submission and successful randomisation could not be confirmed. Further, this analysis was not pre-specified. The PSCR (p.1) presented a comparison of patient characteristics for the subgroup, arguing that it was unlikely that randomisation was affected. The ESC agreed that this was reasonable.

Table 6: Study 588 baseline characteristics of patients with total blood eosinophils ≥ 300 cells/ μ L at baseline

Baseline characteristic	Placebo	MEPO 75 mg IV	MEPO 100 mg SC
N	194	191	191
Age, mean (SD) (years)	42 (12)	42 (12)	42 (12)
BMI, mean (SD) (kg/m ²)	25 (4)	25 (4)	25 (4)
Male gender, n (%)	100 (51)	100 (52)	100 (52)
Race (%)			
White	100 (51)	100 (52)	100 (52)
Asian	1 (0)	1 (0)	1 (0)
Other	1 (0)	1 (0)	1 (0)
Never smoked, n (%)	100 (51)	100 (52)	100 (52)
Smoked, n (%)	1 (0)	1 (0)	1 (0)
Mean duration of asthma, years (SD)	12 (8)	12 (8)	12 (8)
Mean exacerbations in the previous year (SD)	3 (2)	3 (2)	3 (2)
Pre-bronchodilator % predicted FEV ₁ , mean (SD)	85 (15)	85 (15)	85 (15)

Source: mepolizumab Pre-Sub-Committee Response, p.1

Indirect comparison of mepolizumab versus omalizumab

6.14 The results of the indirect comparison between mepolizumab and omalizumab, using standard of care as the common comparator, are presented below.

Table 7: Results of the indirect comparison between mepolizumab (100mg SC) and omalizumab (double-blind trials) with standard of care as the common comparator - rate of clinically significant exacerbations

	MEPO versus SOC			OMAL versus SOC			Indirect RR (95% CI)
	RR (95% CI)	MEPO Exac rate	SOC Exac rate	SOC Exac rate	OMAL Exac rate	RR (95% CI)	
ITT analysis							
Study 588 (32 weeks)	0.47 (0.35, 0.64)	0.83	1.74	-	-	-	-
INNOVATE (28 weeks)	-	-	-	0.91	0.68	0.74 (0.55, 1.00)	-
EXTRA (48 weeks)	-	-	-	0.88	0.66	0.75 (0.61, 0.92)	-
Pooled	0.47 (0.35, 0.64)	-	-	-	-	0.75 ^a (0.63, 0.88)	0.64 (0.45, 0.90)
Primary analysis (≥ 1 exacerbation overlap population)							
Pooled ^b	(██████)	NR	NR	-	-	0.75 ^a (0.63, 0.88)	(██████)
Secondary analysis (≥ 2 exacerbation overlap population) – Excluding EXTRA							
Pooled ^c	(██████)	NR	NR	0.91	0.68	0.74 (0.55, 1.00)	(██████)

Source: Tables 71-72, pp203-204; Tables 73-74, pp206-207; Tables 75-76, pp209-210 of the submission; Table 6.04, p413 of Study 588 CSR; and individual trial papers

CI = confidence interval; Exac = exacerbation; MEPO = mepolizumab; NR = not reported; OMAL = omalizumab; RR = rate ratio; SOC = standard of care; **Bold** = statistically significant result

^a Heterogeneity = 0.931; I² = 0%

^b Study 588 (post hoc subgroup analysis) versus INNOVATE and EXTRA

^c Study 588 (post hoc subgroup analysis) versus INNOVATE

6.15 The submission stated that the results of the indirect comparison indicated that patients treated with mepolizumab (100 mg subcutaneously (SC)) had a statistically significant reduction in the clinically significant exacerbation rate, compared to those treated with omalizumab (results from double-blind trials only) (rate ratio = 0.64; 95% confidence interval: 0.45, 0.90). Results from the primary and secondary analyses suggested that there was no statistically significant difference in the rate of clinically significant exacerbations between mepolizumab and omalizumab. The comparisons were not completely appropriate, as:

- the mepolizumab and omalizumab populations were not completely matched to: (i) the omalizumab PBS restriction; (ii) the proposed mepolizumab PBS restriction; or (iii) each other;
- the definition of clinically significant exacerbation was dissimilar between the mepolizumab and omalizumab trials; and
- the rates of exacerbations presented were for differing time periods.

Comparative harms

6.16 A summary of the adverse events for mepolizumab, standard of care and omalizumab is presented below.

Table 8: Summary of adverse events in the mepolizumab and omalizumab randomised trials

	MEPO versus SOC		OMAL versus SOC	
	MEPO 100 mg SC	SOC	SOC	OMAL
Any adverse event				
Study 588 (32 weeks)	152/194 (78%)	158/191 (83%)	-	-
Study 575 (24 weeks)	57/69 (83%)	61/66 (92%)	-	-
INNOVATE (28 weeks)	-	-	159/237 (67%)	151/245 (62%)
EXALT (32 weeks)	-	-	65/128 (51%)	140/274 (51%)
EXTRA (48 weeks)	-	-	334/420 (80%)	344/428 (80%)
Serious adverse event				
Study 588 (32 weeks)	16/194 (8%)	27/191 (14%)	-	-
Study 575 (24 weeks)	1/69 (1%)	12/66 (18%)	-	-
INNOVATE (28 weeks)	-	-	0	1/245 (< 1%)
EXALT (32 weeks)	-	-	11/128 (9%)	24/274 (9%)
EXTRA (48 weeks)	-	-	44/420 (11%)	40/428 (9%)
Adverse event resulting in withdrawal from trial				
Study 588 (32 weeks)	1/194 (< 1%)	4/191 (2%)	-	-
Study 575 (24 weeks)	3/69 (4%)	3/66 (5%)	-	-
INNOVATE (28 weeks)	-	-	4/237 (2%)	11/245 (5%)
EXALT (32 weeks)	-	-	4/128 (3%)	13/274 (5%)
EXTRA (48 weeks)	-	-	10/420 (2%)	16/428 (4%)

Source: Table 47, p138; Table 83, p221 of the submission

MEPO = mepolizumab; OMAL = omalizumab; SC = subcutaneous; SOC = standard of care

6.17 The most commonly experienced adverse events with mepolizumab therapy included headache (2-7% of patients), nausea (0-5%) and injection site reactions (2-7%).

Benefits/harms

6.18 A summary of the comparative benefits and harms for mepolizumab versus standard of care is presented in the table below.

Table 9: Direct comparison - Summary of comparative benefits and harms for mepolizumab and standard of care (ITT population)

BENEFITS							
	MEPO		SOC	RR (95% CI)	Percent of patients*		RD (95% CI)
	100 mg SC	75 mg IV			MEPO	SOC	
Number of patients with exacerbation/s							
Study 588	64/194	-	105/191	0.60 (0.47, 0.76)	33%	55%	-0.22 (-0.32, -0.12)
	-	70/191		0.67 (0.53, 0.84)	37%		-0.18 (-0.28, -0.09)
Study 575	29/69	-	45/66	0.62 (0.45, 0.85)	42%	68%	-0.26 (-0.42, -0.10)
Study 997	-	70/153	104/155	0.68 (0.56, 0.84)	46%	67%	-0.21 (-0.32, -0.11)
HARMS							
	MEPO 100 mg SC	SOC	RR (95% CI)	Percent of patients*		RD (95% CI)	
				MEPO	SOC		
Headache (number of patients)							
Study 575	5/69	3/66	1.59 (0.40, 6.41)	7%	5%	0.03 (-0.05, 0.11)	
Anxiety (number of patients)							
Study 575	2/69	0	-	3%	0	0.03 (-0.01, 0.07)	
Injection site reaction (number of patients)							
Study 588	14/194	6/191	2.30 (0.90, 5.85)	7%	3%	0.04 (-0.00, 0.09)	

* Duration of exposure: Study 588 = 32 weeks; Study 575 = 24 weeks; Study 997 = 52 weeks

Source: Tables 31-33, pp105-107; Table 50, pp142-143 of the submission; Table 28, p89; Table 6.01, p415 of Study 997 CSR; and calculated during evaluation

CI = confidence interval; ITT = intention-to-treat; IV = intravenous; MEPO = mepolizumab; RD = risk difference; RR = relative risk; SC = subcutaneous; SOC = standard of care; **Bold** = statistically significant result

- 6.19 On the basis of the direct comparison evidence presented by the submission, for every 100 patients treated with mepolizumab in comparison to standard of care:
- Approximately 22 fewer patients would have a clinically significant exacerbation over a maximum duration of exposure of 32 weeks.
 - There are no differences in adverse events.
- 6.20 A summary of the comparative benefits and harms for mepolizumab versus omalizumab, with standard of care as the common comparator is presented below.

Table 10: Indirect comparison - Summary of comparative benefits and harms for mepolizumab and omalizumab

BENEFITS								
	RR (95% CI)	MEPO	SOC	OMAL	RR (95% CI)	Indirect RR (95% CI)		
Rate of clinically significant exacerbations								
Study 588 ^a	0.47 (0.35, 0.64)	0.83	1.74	-	-	-		
INNOVATE ^b	-	-	0.91	0.68	0.74 (0.55, 1.00)	-		
EXTRA ^c	-	-	0.88	0.66	0.75 (0.61, 0.92)	-		
Primary analysis (≥ 1 exacerbation overlap population): Rate of clinically significant exacerbations								
Pooled ^d	[(,)]				0.75 (0.63, 0.88)	[(,)]		
HARMS								
	MEPO ^e	SOC	OMAL	Rel. R (95% CI)	Percent of patients*			RD (95% CI)
Any adverse event (number of patients)								
Study 588	152/194	158/191	-	0.95 (0.86, 1.05)	78%	83%	-	-0.04 (-0.12, 0.04)
INNOVATE		179/237	177/245	0.96 (0.86, 1.06)	-	76%	72%	-0.03 (-0.11, 0.05)
Indirect comparison:				0.99 (0.86, 1.15)				-0.01 (-0.12, 0.10)
Any serious, drug-related adverse event (number of patients)								
Study 588	1/194	1/191	-	0.98 (0.06, 15.63)	< 1%	< 1%		0.00 (-0.01, 0.01)
INNOVATE	-	0	1/245	NE	-	0	< 1	0.00 (-0.00, 0.01)
Indirect comparison:				NE				0.00 (-0.01, 0.01)
Adverse events resulting in withdrawal from trial								
Study 588	1/194	4/191	-	0.25 (0.03, 2.18)	< 1%	2%	-	-0.02 (-0.04, 0.01)
INNOVATE	-	4/237	11/245	2.66 (0.86, 8.24)	-	2%	5%	0.03 (-0.00, 0.06)
Indirect comparison:				0.09 (0.01, 1.06)				-0.05 (-0.09, -0.01)

* Duration of exposure: Study 588 = 32 weeks; INNOVATE = 24 weeks; EXTRA = 48 weeks

Source: Tables 71-72, pp203-204; Tables 73-74, pp206-207; Tables 75-76, pp209-210; Table 83, p221 of the submission; Table 6.04, p413 of Study 588 CSR; Table 43, p107 of Study 588 CSR; and individual trial papers

CI = confidence interval; MEPO = mepolizumab; NE = not estimable; OMAL = omalizumab; RD = risk difference; Rel. R = relative risk; RR = rate ratio; SC = subcutaneous; SOC = standard of care

^a Exacerbation rate per year

^b Exacerbation rate per 24 weeks

^c Exacerbation rate per 48 weeks

^d Study 588 (post hoc subgroup analysis) versus INNOVATE and EXTRA

^e Patients who received mepolizumab 100 mg SC

Clinical claim

Mepolizumab versus standard of care

6.21 The submission described mepolizumab as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over standard of care.

The following issues made the claim of non-inferior comparative safety uncertain:

- the pivotal mepolizumab trials were of moderate lengths (24 to 52 weeks), limiting the availability of long-term safety information; and
- up to 6% of patients developed anti-mepolizumab antibodies, the long-term effects of which in treatment of asthma are unknown. The PSCR (p.3) stated that in most circumstances anti-drug antibodies are of no clinical significance (Barossa, 2007). The PSCR (p.2) also stated that mepolizumab has been tested for up to 12 years in patients with hypereosinophilic syndromes.

- 6.22 Additionally, although the submission identified and attempted to address the differences between the proposed PBS population and the mepolizumab trial populations through post hoc subgroup analyses, there was no comparison between the trial population and Australian patients with severe eosinophilic asthma provided in the submission. It was therefore not clear that the effects of mepolizumab on the trial populations would be replicated in Australian patients.
- 6.23 The ESC considered that the submission's claim of superior comparative effectiveness and non-inferior comparative safety over standard of care was reasonable.
- 6.24 The PBAC considered that the claim of superior comparative effectiveness over standard of care was reasonable.
- 6.25 The PBAC considered that the claim of non-inferior comparative safety over standard of care was reasonable.

Mepolizumab versus omalizumab

- 6.26 The submission described mepolizumab as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over omalizumab for patients eligible for both medications.
The claim of non-inferior effectiveness might not be adequately supported as:
- the analysis was an indirect comparison in which the mepolizumab and omalizumab populations were not completely matched to: (i) the omalizumab PBS restriction; (ii) the proposed mepolizumab PBS restriction; or (iii) each other.
 - the definition of clinically significant exacerbation was dissimilar between the mepolizumab and omalizumab trials.
 - the rates of exacerbations presented were for differing time periods.
- 6.27 The claim of non-inferior comparative safety may be difficult to interpret as:
- the omalizumab trials presented only limited safety information making the comparison of adverse events difficult.
- 6.28 The ESC considered that the submission's claim of non-inferior comparative effectiveness and non-inferior comparative safety over omalizumab appeared to be reasonable.
- 6.29 The PBAC considered that the claim of non-inferior comparative effectiveness with omalizumab was reasonable.
- 6.30 The PBAC considered that the claim of non-inferior comparative safety with omalizumab was reasonable.

Economic analysis

- 6.31 The submission presented two economic analyses:
1. A cost-effectiveness analysis versus standard of care; and
 2. A cost-minimisation analysis versus omalizumab.

The submission then used population utilisation to derive a weighted dispensed price for maximum quantity (DPMQ).

Cost-effectiveness analysis

- 6.32 The cost-effectiveness analysis of mepolizumab versus standard of care was based on the direct evidence and the claim of clinical superiority. The submission presented a Markov model with six health states: (i) mepolizumab first 32 weeks; (ii) mepolizumab responders; (iii) standard of care first 32 weeks; (iv) standard of care beyond 32 weeks; (v) asthma-related death; and (vi) all-cause mortality.
- 6.33 In the model, continuation criteria were applied at 32 weeks, and were defined as a requirement to demonstrate a reduction of at least 0.5 in the Asthma control questionnaire (ACQ-5) score as compared to baseline (this is consistent with the continuation criteria in the proposed restriction). The ESC noted that if this continuation criterion was not effectively applied in practice, the ICER would be higher than estimated in the submission (assuming that patients not meeting this criterion have higher exacerbation rates than patients who do meet this criterion).
- 6.34 Patients receiving mepolizumab who failed to meet the requirement would transition to the 'standard of care beyond 32 weeks' health state. These patients immediately incurred standard of care associated exacerbation rates and health status.
- 6.35 Post application of the continuation criteria at 32 weeks, it was assumed that a small proportion of patients discontinued mepolizumab treatment (█% per four-week cycle), transitioning to the 'standard of care beyond 32 weeks' health state. The ESC noted that if in practice patients remained on treatment despite not meeting the continuation criterion, the ICER would be higher than estimated in the submission.
- 6.36 The submission assumed that all patients would discontinue mepolizumab treatment after ten years. Patients could experience an exacerbation in all asthma-related health states; the rate depended on treatment received.
- 6.37 A rate of 1.13% for mortality following an exacerbation requiring hospitalisation was derived from a relevant published study, but a mortality probability of 0.43% for non-hospitalised exacerbations was derived from calculations using data from disparate sources. The ESC considered that the magnitude of difference between these mortality estimates (i.e. risk of mortality is more than doubled if an exacerbation requires hospitalisation compared to exacerbation without hospitalisation) appeared infeasible, and a review of similar parameter estimates from published asthma cost-effectiveness models should have been presented to demonstrate feasibility.
- 6.38 The model structure is presented in the table below.

Table 11: Summary of model structure and rationale

Component	Summary
Time horizon	Lifetime horizon in the model base case versus 32 weeks in Study 588.
Outcomes	Life years gained (LYG) and quality-adjusted life years (QALY).
Methods used to generate results	Markov model that used a cohort expected value analysis.
Health states	Four asthma related health states; two mortality health states.
Cycle length	Four weeks

Source: Compiled during the evaluation

- 6.39 A summary of the key drivers of the cost-effectiveness model are presented below.

Table 12: Key drivers of the model

Description	Method/Value	Impact
Time horizon	Lifetime; assumed from 32 week trial duration	Moderate (favoured MEPO)
Time horizon	The MEPO group gains additional QALYs to around age 120 years.	Low (favoured MEPO)
Use of ACQ-5 score in CC	Change of > 0.5 from baseline required	High (favoured MEPO)
Population included	Use of post hoc subgroup from Study 588	Moderate (favoured MEPO)
Intervention costs for ICS/LABA	Model error: costs applied inconsistently and inappropriately for the two treatment arms	High (favoured MEPO)
Respiratory specialist cost	Underestimated	Low (favoured MEPO)
Exacerbation-related mortality	High mortality rate for non-hospitalised exacerbations	Moderate (favoured MEPO)
Exacerbation types	Aggregate percentages do not align with exacerbation data by treatment group	Low (favoured MEPO)
Utilities	Derived from SGRQ scores	High (favoured MEPO)
Utilities	Exacerbation duration 28 days; trial data durations: non-hospitalized exacerbation 10 to 13 days; hospitalized exacerbation 21 days.	Low (favoured MEPO)

Source: Compiled during the evaluation

ACQ-5 = Asthma control questionnaire; CC = continuing criteria; MEPO = mepolizumab; SGRQ = St George's respiratory questionnaire

- 6.40 St George's respiratory questionnaire (SGRQ) scores captured in Study 588 were converted to Euroqol 5-dimension 3-level instrument (EQ-5D-3L) utility values using a mapping algorithm, as described in Starkie (2011). The algorithm had precision issues, meaning it might have been more appropriate to use EQ-5D-3L scores obtained from Study 997 in the base case.
- 6.41 The choice of MBS item 105 (\$██████) does not fit with usual physician practice: Initial Item 110 (\$██████) and subsequently Item 116 (\$██████) should have been used. The total cost difference is \$██████.
- 6.42 Aggregate exacerbation rates and by treatment group are presented below. It was not clear where the value for hospitalised exacerbations was derived from.

Table 13: Summary of health outcomes

Exacerbations requiring:	As per model	For those on SOC	For those on MEPO 100 mg SC
OCS burst	█ %	█ %	█ %
ED visit	█ %	█ %	█ %
Hospitalisation	█ %	█ %	█ %

Source: Compiled by evaluators from Attachment D3, Table 6.01 of Study 588 CSR

6.43 The results of the economic model are presented in the table below.

Table 14: Results of the economic evaluation – per patient

	Mepolizumab	Standard of care	Increment
Total costs	\$ █	\$62,270	\$ █
Total LYG: undiscounted	30.39	29.87	0.52
discounted	14.86	14.63	0.23
Total QALYs: discounted	10.87	10.34	0.53
Incremental cost per LYG: undiscounted			\$ █
discounted			\$ █
Incremental cost per QALY: discounted			\$ █

Source: Table 153, p344 of the submission

LYG = life year gained; QALY = quality-adjusted life year

6.44 The economic model estimated an incremental cost-effectiveness ratio (ICER) of \$45,000 - \$75,000 per quality-adjusted life year (QALY) gained. The estimated ICER could be unreliable due to:

- extrapolation of exacerbation rates from Week 16 to 32 of Study 588 to the life duration of the model might have been unreliable; and
- the use of a modelled algorithm to convert SGRQ scores to EQ-5D-3L utility values.

6.45 The 'no continuation criteria' sensitivity analysis is not a true analysis of no continuation criteria because for this sensitivity analysis it is assumed that all patients meet the requirement for a 0.5 reduction in ACQ-5 score at 32 weeks. In reality, the additional patients receiving treatment under a 'no continuation criteria' scenario would have worse performance because they did not respond to treatment.

6.46 In most of the sensitivity analyses in which patients remain longer in the treatment state (e.g. higher percentage of patients continuing treatment, zero discontinuation rate, no continuation criterion), the ICER increases. This is because the exacerbation rates in the SOC arm decrease after 16 weeks (in aggregate from █% to █%). This means MEPO is more cost-effective in the first 32 weeks than in the period after 32 weeks, after the application of the continuation criterion.

6.47 The ICER decreases in the longer treatment duration sensitivity analysis because the SOC intervention costs are applied to all SOC patients who are alive and not experiencing an exacerbation. MEPO intervention costs are only applied to MEPO patients on treatment, which is a small proportion by year 10.

6.48 A fundamental model error is that the intervention costs were applied inconsistently and inappropriately for the two treatment arms:

- a. For mepolizumab, patients would receive LABA/ICS when they were also on mepolizumab treatment. As soon as patients discontinued mepolizumab treatment they also discontinued LABA/ICS treatment.
- b. For standard of care arm, patients would receive LABA/ICS for ten years. LABA/ICS costs should not have been included in the intervention costs. This favoured mepolizumab.

6.49 The Pre-PBAC Response (p.3) accepted that there was an error in the application of LABA/ICS costs and accepted the recalculation of treatment costs, noting that this increased the ICER to 45,000/QALY - \$75,000/QALY..

6.50 Sensitivity analyses are presented below for the ESC’s respecified base case where the LABA/ICS costs were excluded from the intervention costs as it was considered that all patients would have continued background treatment with LABA/ICS.

Table 15: Results of key sensitivity analyses – per patient: Analyses re-run with error in model corrected

Sensitivity analyses	Δ costs	Δ QALY	ICER
Base case	\$ [redacted]	0.53	\$ [redacted]
Error corrected and LABA/ICS costs not double counted in treatment or SOC arms ^a	\$ [redacted]	0.53	\$ [redacted]
Patient population (base case = eosinophil ≥ 300 mg in last 6 weeks) ITT population (eosinophil ≥ 150 in last 6 weeks or ≥ 300 mg in last 12 months)	\$ [redacted]	0.35	\$ [redacted]
Time horizon (base case = lifetime)			
10 years	\$ [redacted]	0.43	\$ [redacted]
30 years	\$ [redacted]	0.52	\$ [redacted]
Treatment duration (base case = 10 years)			
5 years	\$ [redacted]	0.39	\$ [redacted]
20 years	\$ [redacted]	0.62	\$ [redacted]
% mepolizumab patients continuing treatment (base case = 0.60)			
0.53	\$ [redacted]	0.48	\$ [redacted]
0.67	\$ [redacted]	0.58	\$ [redacted]
Mepolizumab discontinuation rate (base case = [redacted])			
0.0000	\$ [redacted]	0.78	\$ [redacted]
0.0098	\$ [redacted]	0.52	\$ [redacted]
Continuation criteria (base case = ACQ-5 score change of > 0.5)			
None	\$ [redacted]	0.61	\$ [redacted]
ACQ-5 score change of ≥ 1.5	\$ [redacted]	0.76	\$ [redacted]
<i>Asthma-related deaths:</i>			
	Exac + OCS burst	Exac + ED visit	Exac + hospital
Base case	0.0043	0.0043	0.0113
Lower 95% CI	0.0039	0.0039	0.0090
Upper 95% CI	0.0047	0.0047	0.0140
<i>In ED and hosp</i>	0.0000	0.0043	0.0113
<i>Only for hospital</i>	0.0000	0.0000	0.0113
Utilities (SGRQ replaced with EQ-5D scores from Study 977):			
	MEPO ≤ 32 wks	SOC ≤ 32 wks	MEPO > 32 wks
Base case	[redacted]	[redacted]	[redacted]
EQ-5D-3L	[redacted]	[redacted]	[redacted]
	\$ [redacted]		
		0.38	\$ [redacted]

Source: Tables 154-155, p345-347 of the submission; and Section D.1Workbook_Australian_MEPO model_30.10.2015.xlsm
 ACQ-5 = Asthma control questionnaire; CI = confidence interval; ED = emergency department; EQ-5D = Euroqol 5-dimension instrument; EQ-5D-3L = Euroqol 5-dimension 3-level instrument; Exac = exacerbation; ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; MEPO = mepolizumab; OCS = oral corticosteroid; QALY = quality-adjusted life year; SGRQ = St George’s respiratory questionnaire; SOC = standard of care; wks = weeks

^a The LABA/ICS costs were double counted in the base case, assuming that all patients would receive this as a background

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therapy and it was added when the patients would receive the intervention (i.e. mepolizumab + SOC or SOC).

- 6.51 The Pre-PBAC Response (p.3) presented a revised base case ICER of \$45,000/QALY - \$75,000/QALY applying exacerbation related mortality derived from a “conservative interpretation of OMA’s economic model (application of 1.13% morality risk across all exacerbation types) and correction of ICS/LABA costing error”.
- 6.52 The results of the sensitivity analyses indicated that the model was most reactive to the population (eosinophil count as per the proposed TGA indication compared to as per the proposed PBS restriction), source of utility values, continuation criteria and asthma-related deaths.

Cost-minimisation analysis

- 6.53 The cost-minimisation analysis of mepolizumab versus omalizumab was based on the indirect evidence and the claim of clinical non-inferiority.
- 6.54 The equi-effective doses were estimated in the submission as mepolizumab 100 mg SC every four weeks and omalizumab [REDACTED] mg SC every four weeks. The submission incorrectly used utilisation data to calculate the equi-effective dose. Using baseline characteristics from the INNOVATE trial, which was used in the indirect comparison, the equi-effective dose of omalizumab was [REDACTED] mg SC every four weeks. Although the PSCR (p.3) argued that “it is inappropriate to base the equi-effective dose of MEPO vs. OMA on OMA dosing from studies that do not reflect actual OMA efficacy or usage on the PBS”, the ESC agreed with the Commentary, noting that preferred data source for the estimation of equi-effective doses is the clinical trial data. The submission’s deviation from the preferred approach was not well justified.

Table 16: Cost-minimisation analysis for mepolizumab and omalizumab

	AEMP	Cost/mg	Submission	Equi-effective dose from clinical trial data
Omalizumab				
AEMP (PBS item 10109C):				
150 mg/mL	\$410	\$2.73	-	-
75 mg/0.5 mL	\$205		-	-
Average monthly dose per patient	-	-	[REDACTED] mg	[REDACTED] mg
Average monthly cost (AEMP)	-	-	\$ [REDACTED]	\$ [REDACTED]
Mepolizumab				
Monthly dose per patient	-	-	100 mg	
Average monthly cost (AEMP/public hospital)	-	-	\$ [REDACTED]	\$ [REDACTED]

Source: Tables 160-161, p352 of the submission; and *calculated during evaluation*
AEMP = approved ex-manufacturer price; PBS = Pharmaceutical Benefits Scheme

- 6.55 A weighted analysis using trial data from the IDEAL Study, rather than utilisation data, was used to calculate the DPMQ of mepolizumab. The IDEAL Study was an unpublished cross-sectional international study that aimed to describe the baseline patient and disease characteristics of the severe asthma population that was determined as having met eligibility criteria for biologic treatment.

Table 17: Weighted DPMQ for mepolizumab

	Price	Proportion	Weighted DPMQ (Public)	Weighted DPMQ (Private)
Cost-minimised price versus OMAL	a) █████ mg ^a : \$ █████ b) █████ mg ^b : \$ █████	█████%	a) \$ █████ b) \$ █████	a) \$ █████ ^c b) \$ █████
Cost-effective price versus SOC	\$ █████	█████%		

Source: Tables 162-163, pp353-354 of the submission

DPMQ = dispensed price for maximum quantity; OMAL = omalizumab; SOC = standard of care

^a Equi-effective dose of omalizumab as estimated in the submission

^b Equi-effective dose of omalizumab as estimated by using the INNOVATE trial

^c Addition of \$ █████ dispensing fee (corrected private DPMQ = \$ █████)

- 6.56 Calculations for the weighted price of mepolizumab were not appropriate as:
- when the trial-based equi-effective dose of omalizumab was used, the weighted prices of mepolizumab were calculated as \$ █████ (approved ex-manufacturer price (AEMP)/public DPMQ) and \$ █████ (private DPMQ);
 - the estimated comparator proportions might not have been accurate as trial data, rather than utilisation data, was used; and
 - the addition of a \$ █████ dispensing fee to the public price to calculate the private price for a Section 100 medication was not correct – the corrected private DPMQ would be \$ █████.

Drug cost/patient/year: \$ █████

- 6.57 The cost of mepolizumab per patient per month is \$ █████, and \$ █████ per patient per year. Mepolizumab is given every four weeks and the submission assumed 13 doses per year. Initial treatment is 32 weeks. Patients who meet the continuation criteria receive further treatment.

Estimated PBS usage & financial implications

- 6.58 The submission was considered by DUSC.
- 6.59 The submission used both epidemiological and market share approaches to estimate the expected utilisation of mepolizumab:
- A market share approach was used for patients eligible for both mepolizumab and omalizumab, and in whom mepolizumab would replace omalizumab;
 - An epidemiological approach was used for patients eligible for both mepolizumab and omalizumab, and in whom mepolizumab would not replace omalizumab; and
 - An epidemiological approach was used for patients eligible for mepolizumab only.
- 6.60 The population in whom mepolizumab would replace omalizumab was calculated using DUSC utilisation data and clinical criteria from the IDEAL Study. The epidemiological approach first calculated the number of patients with severe, uncontrolled asthma who were compliant with inhaled corticosteroids/long-acting beta agonists (ICS/LABA) therapy, using predominantly Australian data sources. IDEAL Study data was then used to ascertain the number eligible for mepolizumab.
- 6.61 Uptake rates were assumed for all populations.

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Patients eligible for MEPO					
Uptake					
eligible for MEPO and OMAL, treated with OMAL	10%	20%	20%	20%	20%
not treated with OMAL	1%	1%	1%	1%	1%
eligible for MEPO only	2%	2%	2%	2%	2%
Patients initiating MEPO			2		
Patients meeting CC					
Patients continuing MEPO					
Total MEPO prescriptions					
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost to MBS	\$	\$	\$	\$	\$
Estimated total net cost (submission base case; mepolizumab DPMQ \$)					
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$
Estimated total net cost (mepolizumab DPMQ calculated by evaluation \$)					
Net cost to PBS/RPBS/MBS	\$	\$	\$	\$	\$

Source: Table 177, p374; Table 190, p389 of the submission

AEMP = approved ex-manufacturer price; CC = continuation criteria; MBS = Medicare Benefits Schedule; MEPO = mepolizumab; OMAL = omalizumab; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted table above shows that at year 5, the estimated number of patients would be 10,000 – 50,000 and the net cost to PBS would be less than \$10 million.

- 6.62 The submission estimated that the addition of mepolizumab to the PBS/RPBS would cost the government \$ million in Year 5 of listing. When the DPMQ is adjusted to reflect the evaluation’s recalculation of the equi-effective dose (see 6.35, above), the estimated total net cost of mepolizumab is \$ million in year 5 of listing.
- 6.63 The Commentary stated that the estimated financial impact of mepolizumab may be greater or less given that:
- the clinical criteria (e.g. eosinophil levels), derived from patients in the IDEAL Study, might not be representative of the Australian severe asthma population;
 - the proportion of patients treated with an ICS/LABA combination product (35% from 2008-2009 Bettering the Evaluation And Care of Health (BEACH) general practice data might not be accurate. More recent data from an Australian study (Reddel 2015) suggested up to 49.6% of asthma patients had used an ICS/LABA inhaler in the past 12 months;
 - uptake rates were assumed;
 - the proportion of patients meeting the continuation criteria (%), derived from Study 588, might not reflect Australian rates; and
 - discontinuation rates, derived from the extension study (%), Study 661, might not reflect rates in the Australian population.
- 6.64 Sensitivity analyses suggested that the financial estimates were sensitive to the percentage of patients on optimised high-dose ICS/LABA therapy and the uptake rates of mepolizumab.

- 6.65 While DUSC did not agree with all of the submission’s inputs to the financial model, the total estimate of use over the five years may be reasonable. However, DUSC considered the Year 1 estimates presented in the submission to be under-estimated. The main issues were:
- The population clinical criteria, derived from the IDEAL study, might not be representative of the Australian severe asthma population.
 - DUSC considered it more straightforward to use a prevalence only approach for estimating PBS usage and financial implications of mepolizumab.
 - The proportion of patients treated with an inhaled corticosteroid/long acting beta agonist (ICS/LABA) combination product (35%), might be underestimated. DUSC considered the Reddel (2015) estimate for patients using an ICS/LABA therapy (49.6%) as more appropriate than the 2008-2009 BEACH general practice data.
 - DUSC considered the application of a continuation rate of 80% for mepolizumab would be a more appropriate estimate, consistent with the omalizumab continuation rate in practice.
- 6.66 Presented below are revised estimates as provided by DUSC which:
- use a prevalence only approach;
 - use a higher estimate of asthma patients treated with ICS/LABA combination from the Reddel (2015)¹ study;
 - use a grouped cohort of patients with eosinophils \geq 300 cells/mL and therefore eligible for mepolizumab (33.5%) instead of three separate cohorts;
 - use an uptake rate of 2%; and
 - use a continuation rate of 80% based on omalizumab continuation rate².

Table 19: Net financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated total net cost (Submission base case; mepolizumab DPMQ \$ [redacted])					
Net cost to PBS/RPBS/MBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Estimated net cost to PBS/RPBS (MEPO DPMQ \$ [redacted]) (COM.15)					
Net cost to PBS/RPBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Estimated net cost to PBS/RPBS (MEPO DPMQ \$ [redacted]) (DUSC re-estimates)					
Net cost to PBS/RPBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

Source: Table 6, 5.05.DUSC ADV.8, modified from table 16; 5.05.COM.15
MEPO = mepolizumab

The redacted table above shows that the net cost to PBS would be less than \$10 million.

- 6.67 The Pre-PBAC Response (p.3) accepted most of DUSC’s comments regarding the structure and inputs to the financial model, however the sponsor did not accept the application of omalizumab’s real world continuation rate of 80%, as the sponsor claimed that this should be treatment specific.

Quality Use of Medicines

¹ Reddel et al. Asthma control in Australia: a cross-sectional web-based survey in a nationally representative population. Med J Aust 2015; 202 (9): 492-496.

² Public release document, DUSC utilisation analysis, June 2014. Found at: <http://www.pbs.gov.au/industry/listing/participants/public-release-docs/omalizumab/omalizumab-24-month-review.pdf>

- 6.68 DUSC considered that systemic corticosteroids can reduce the blood eosinophil count in patients, which may affect the eligibility of some patients for mepolizumab.
- 6.69 The requested restriction details that a patient must be under the same care of the same physician for at least 12 months. DUSC considered this may affect equity for rural patients due to reduced access to physicians.

Financial Management – Risk Sharing Arrangements

- 6.70 The Sponsor intends to request a Special Price Arrangement during price negotiations, should mepolizumab receive a positive recommendation from PBAC.

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

7 PBAC Outcome

- 7.1 The PBAC rejected the listing of mepolizumab on the basis of high and uncertain cost-effectiveness in the comparison with standard of care, and inappropriate equi-effective doses proposed in the cost-minimisation analysis against omalizumab.
- 7.2 The PBAC accepted that mepolizumab had a clinical place in the treatment of eosinophilic asthma, noting advice received from the TSANZ clarifying that there is sufficient distinction to allow recognition and application of different therapies to this distinct asthma phenotype.
- 7.3 The PBAC did not agree with the submission's method of estimating the equi-effective doses for mepolizumab and omalizumab, which derived the omalizumab dose from utilisation data rather than using the trial based doses. The omalizumab dose of [REDACTED] mg from the utilisation data was substantially larger than the [REDACTED] mg derived from the clinical trial data, and the PBAC noted that the submission's deviation from the preferred approach resulted in a substantial increase in the price of mepolizumab estimated.
- 7.4 The PBAC considered the following with regard to the requested restriction:
- the restriction for mepolizumab should stipulate that it would not be permitted for use in combination with omalizumab;
 - the definition of failure to optimised therapy be consistent with omalizumab.
- 7.5 The PBAC accepted SOC and omalizumab as appropriate comparators.
- 7.6 The PBAC considered that the clinical comparison of mepolizumab versus SOC was reasonably reliable, noting the three direct clinical trials of mepolizumab versus SOC. The PBAC considered the indirect comparison of mepolizumab versus omalizumab, using standard of care as the common reference, to be substantially more uncertain due to differences in the trials, including time periods over which exacerbations rates were reported and placebo event rates.
- 7.7 The PBAC considered that the claim of superior comparative effectiveness and non-inferior comparative safety to standard of care was reasonable.

- 7.8 The PBAC considered that the claim of non-inferior comparative effectiveness and non-inferior comparative safety to omalizumab was reasonable, noting uncertainties with the indirect comparison.
- 7.9 The PBAC agreed with the ESC's view that several assumptions and inputs into the economic model in the cost-effectiveness analysis versus SOC highly favoured mepolizumab, including the source of the utilities, use of ACQ-5 score in the continuation criteria, and the error in the model regarding intervention costs for ICS/LABA (corrected by the ESC). The PBAC noted that the ESC's revised base case, corrected for errors, was \$45,000/QALY - \$75,000/QALY. The Pre-PBAC Response accepted the corrected errors, and further applied a 1.13% mortality risk across all exacerbation types (as opposed to the original model which applied a 1.13% mortality risk following an exacerbation requiring hospitalisation and a 0.43% mortality risk following an exacerbation requiring an ED visit or OCS burst) which reduced the sponsor's base case ICER to \$45,000/QALY - \$75,000/QALY, however the PBAC considered that the model could not be relied upon given the substantial variation in the outputs.
- 7.10 The PBAC agreed with the DUSC's estimates of the financial implications, noting that although the DUSC considered Year 1 estimates to be underestimated, the DUSC considered the total estimate of use over five years may be reasonable.
- 7.11 The PBAC proposed that a pragmatic approach forward would be a minor resubmission presenting a cost-minimisation against omalizumab using the trial based equi-effective doses. Should a resubmission wish to present a cost-effective analysis, this would need to be provided as a major submission to allow for evaluation.
- 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

GSK is disappointed with the outcome and is reviewing the PBAC recommendation to inform a resubmission. GSK is committed to working with the PBAC and the Department to ensure severe asthma patients can access mepolizumab through the PBS.