

7.04 MEPOLIZUMAB

Lyophilised powder for subcutaneous injection, 100 mg, Nucala®, GlaxoSmithKline

1 Purpose of Application

- 1.1 The minor resubmission 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 Background

- 2.1 This was the second submission for PBS listing of mepolizumab. The PBAC considered a major submission in March 2016. 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.
- 2.2 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.
- 2.3 The minor resubmission sought to address the PBAC's concerns regarding inappropriate equi-effective doses proposed in the cost-minimisation analysis of mepolizumab against omalizumab. The main difference in the minor resubmission compared to the previous submission was in the economic analysis, where a revised cost-minimisation analysis was presented. Corresponding updates to the financial estimates were also presented. Otherwise the information presented is mostly unchanged from that previously considered by the PBAC.
- 2.4 Table 1 provides an overview of the issues addressed in the minor resubmission.

Table 1: Overview of the issues addressed in the minor resubmission

March 2016 PBAC comments	Approach adopted in the minor resubmission
[Paragraph 7.4] The PBAC considered the following with regard to the requested restriction: i) the restriction for mepolizumab should stipulate that it would not be permitted for use in combination with omalizumab; and ii) the definition of failure to optimised therapy be consistent with omalizumab.	The requested restriction was revised to include the PBAC recommendations.

<p>[Paragraph 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....the PBAC considered that the model could not be relied upon given the substantial variation in the outputs.</p>	<p>A SOC cost-effectiveness comparison was not presented, nor was a SOC comparative price requested.</p>
<p>[Paragraph 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.</p>	<p>Although a revised cost-minimisation analysis was presented in the minor resubmission, trial-based equi-effective doses were not used.</p>
<p>[Paragraph 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 DUSC utilisation data rather than using the trial based doses. The omalizumab dose of 506 mg from the DUSC utilisation data was substantially larger than the 257 mg derived from the clinical trial data.</p>	<p>The commentary calculated equi-effective dose of 257 mg was not adopted, as according to the resubmission, it was incorrectly calculated. The equi-effective dose of 257 mg calculated in the Commentary was based on the minimum, rather than average dose.</p> <p>The resubmission proposed an equi-effective omalizumab dose of 437 mg.</p> <p>The cost-minimisation analysis was revised to incorporate the incremental cost of administration and monitoring associated with omalizumab.</p>
<p>[Paragraph 7.10] The PBAC agreed with the DUSC 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.</p>	<p>Revised financial estimates incorporating DUSC suggested revisions were provided.</p>

Source: Table 1, p2 of the resubmission; and Section 7, pp22-23 of the March 2016 PBAC minutes

DUSC = Drug Utilisation Sub-Committee; ESC = Economic Sub-Committee; IgE = immunoglobulin E; ITT = intention to treat; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = public summary document; SOC = standard of care

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

3 Requested listing

- 3.1 The proposed listing was unchanged from the previous submission, with the exception of the modifications proposed in the PBAC minutes.

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

4 Clinical place for proposed therapy

- 4.1 The clinical place in therapy proposed in the March 2016 PBAC submission for mepolizumab was accepted by the PBAC and was unchanged in the minor resubmission.

5 Comparator

- 5.1 The comparators, SOC and omalizumab, were accepted by the PBAC in March 2016. The updated economic analysis in the minor resubmission was a comparison to omalizumab. The PBAC considered this was appropriate.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

- 6.3 No new clinical data were presented in the minor resubmission.

Clinical claim

- 6.4 The previous 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.
- 6.5 The PBAC recalled that they had previously considered that the claims of non-inferior comparative effectiveness and safety were reasonable.

Economic analysis

Estimation of equi-effective doses

- 6.6 The March 2016 major submission had estimated the equi-effective doses for mepolizumab and omalizumab based on utilisation data for omalizumab rather than using the trial based doses. The PBAC minutes noted that the preferred data source for the estimation of equi-effective doses is the clinical trial data, and that the submission's deviation from the preferred approach was not well justified. The PBAC recommended that a minor resubmission presenting a cost-minimisation analysis that used the trial based equi-effective doses would be appropriate.
- 6.7 The minor resubmission stated that the equi-effective dose of 257 mg omalizumab, as proposed in the March 2016 commentary using INNOVATE trial data, was incorrect as this represented the minimum omalizumab dose, rather than the average dose. This comment was valid; the omalizumab dose used for the calculations was the minimum dose.

- 6.8 The resubmission claimed that the INNOVATE intention-to-treat (ITT) population was not representative of the omalizumab population who accessed treatment via the PBS. This was based on information from the November 2015 public summary document for omalizumab. Approximately 18% of the INNOVATE ITT and the open-label EXALT study (Study 2425) populations met the recommended PBS omalizumab restriction criteria (see Table 2).

Table 2: Proportion of the omalizumab trial population that meets the recommended PBS restriction – PSD omalizumab, November 2015

	ITT population (INNOVATE n = 419; EXALT, n = 400)	Patients meeting current omalizumab PBS criteria (including IgE ≥ 76 IU/mL)	Patients meeting PBAC recommended omalizumab PBS criteria (including IgE ≥ 30 IU/mL)
N	819	118 (14%)	146 (18%)
IgE, mean	213 IU/mL	242 IU/mL	206 IU/mL

Source: Table 3, p6 of the resubmission

IgE = immunoglobulin E; ITT = intention to treat; PBAC = Pharmaceutical Benefit Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSD = public summary document

- 6.9 The minor resubmission suggested that the derivation of the equi-effective dose from the ITT population of the INNOVATE trial was inappropriate, as:
- the omalizumab PBS population had substantially higher IgE, weight and asthma severity than the INNOVATE ITT population; and
 - the IgE range permitted in INNOVATE trial (30-700 IU/mL) was now redundant as the baseline total IgE in the omalizumab product information had been increased to ≤ 1,300 IU/mL. The resubmission claimed that IgE levels are the most important determinant in calculating the correct omalizumab dosage.
- 6.10 The minor resubmission noted the clinical claim that mepolizumab was non-inferior to omalizumab was based on indirect comparisons that provided the best 'like with like' comparison, not the best representative comparison of the current omalizumab PBS population nor the requested mepolizumab population. This was due to a lack of access to omalizumab patient level data. The minor resubmission considered that it was reasonable to assume that the clinical claim from the 'like with like' comparison of a milder population would be applicable in the more severe omalizumab PBS population and the requested mepolizumab PBS population.
- 6.11 The minor resubmission investigated estimating the equi-effective dose of omalizumab from the subgroup of patients with severe asthma within the INNOVATE population. However, dosing data relating to severe asthma patients was unable to be located.
- 6.12 The resubmission stated that the DUSC utilisation data were based on an omalizumab patient population that no longer directly represented the current omalizumab PBS populations. This was due to:
- the registration and PBS listing of a 75 mg omalizumab vial which eliminated wastage; and
 - the extension of the IgE range from ≥ 76 IU/mL to ≥ 30 IU/mL, which resulted in patients with less severe asthma receiving omalizumab and reducing the mean dose.

- 6.13 Adjusting for the above factors, the mean dose of omalizumab was estimated by the submission to be 437 mg per patient per four weeks (see Table 3).

Table 3: Mean doses of omalizumab per patient per four weeks

	DUSC utilisation data		Inclusion of 75 mg vial	Inclusion of 75 mg vial + IgE of 30-75 IU/mL
	150 mg vial		150 mg + 75 mg vials	150 mg + 75 mg vials
	Wastage	No wastage	No wastage	No wastage
Mean	575 mg	506 mg	506 mg	437 mg

Source: Table 5, p8 of the minor resubmission

DUSC = Drug Utilisation Sub-Committee; IgE = immunoglobulin E

- 6.14 The minor resubmission presented two alternate approaches for the estimation of the equi-effective doses, both of which relied on the DUSC utilisation data¹:

- **Approach 1:** Midpoint (mean) of the INNOVATE ITT (broad population) and DUSC utilisation data doses (severe population) –
Result = (INNOVATE 398 mg + DUSC 506 mg)/2 = **452 mg per patient per four weeks**
- **Approach 2:** Modification of DUSC utilisation data to account for change to omalizumab vial sizes and population expansion based on data derived from INNOVATE –
Result = mean DUSC dose of 506 mg revised to include 75 mg vial and estimated dosing and number of patients with IgE of 30-76 IU/mL based on INNOVATE data = **437 mg per patient per four weeks**

- 6.15 The minor resubmission proposed using Approach 2 for the equi-effective dose:

100 mg mepolizumab every four weeks = 437 mg omalizumab per four weeks

- 6.16 The PBAC noted the arguments presented in the minor resubmission to support the use of utilisation data in the estimation of equi-effective doses, but maintained their previous view that the equi-effective doses should be derived from the clinical trial data. The Committee noted that the mean omalizumab dose from the INNOVATE trial was 398 mg. Therefore the PBAC considered that the appropriate equi-effective doses were:

100 mg mepolizumab every four weeks = 398 mg omalizumab per four weeks

Cost-minimisation analysis

- 6.17 The minor resubmission based the cost-minimisation approach on the equi-effective doses of mepolizumab and omalizumab. Cost offsets were incorporated for administration, the treatment of adverse events (anaphylaxis), and longer supervision due to the potential of anaphylaxis with omalizumab. In the previous submission, for

¹ Drug utilisation subcommittee (DUSC). Omalizumab: 24 month predicted versus actual analysis. Public release document, June 2014 DUSC meeting. Available at: <http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/omalizumab>

the cost-minimisation analysis compared with omalizumab only the drug costs were included. The PBAC agreed that the cost offsets presented in the minor resubmission's cost-minimisation analysis were reasonable.

- 6.18 Table 4 outlines the estimated omalizumab price per mg and the corresponding annual cost, calculated in the minor resubmission. The minor resubmission acknowledged that omalizumab has a Special Pricing Arrangement and therefore could not calculate the annual omalizumab cost based on the effective price.

Table 4: Equi-effective 4-weekly and annual cost of omalizumab

Strength	PBS code	DPMQ	Cost per mg	4-weekly dose	4-weekly cost	Annual cost
150 mg/mL	10109C	\$410	\$2.73	437 mg	\$1,194.47	\$15,582.11
75 mg/mL	10118M	\$205	\$2.73			

Source: Tables 7-8, p13 of the resubmission

DPMQ = dispensed price for maximum quantity; PBS = Pharmaceutical Benefits Scheme

- 6.19 Mepolizumab is administered as a single 100 mg subcutaneous injection every four weeks. The maximum dose of omalizumab (750 mg) and a proportion of the 450 mg and 600 mg doses are required to be split into two equal doses to be administered every 2 weeks. This results in additional administration costs with omalizumab.
- 6.20 Using the DUSC utilisation data, it was calculated that █% of omalizumab patients required two-weekly dosing. When this was modified to include patients with IgE levels of 30-75 IU/mL, the proportion requiring two-weekly dosing was █%. The minor resubmission assumed that for patients receiving two-weekly omalizumab the additional doses would be administered by a nurse and the associated cost is \$█ (█ x \$8.20 [MBS Item 82200]) per patient per year.
- 6.21 The minor resubmission stated that omalizumab is associated with an increased risk (prevalence = 0.2%) of anaphylaxis. In contrast, there were no reports of anaphylaxis attributable to mepolizumab across three placebo-controlled studies and two open-label extension studies (N = 1,931).
- The Thoracic Society of Australia and New Zealand² also recommends that omalizumab patients receive an automated adrenaline syringe with instructions on how and when to use. The minor resubmission assumed that all patients treated with omalizumab would need a new syringe every █, based on the approximate shelf-life. This might not be reasonable, because in clinical practice patients treated with mepolizumab might still be given an adrenaline syringe as a prophylaxis.
 - The Thoracic Society of Australia and New Zealand recommends that omalizumab patients are monitored on site for two hours post-injection. The resubmission therefore proposed that an additional cost of \$33.80 (MBS item 82210, 20 minutes of nurse attendance) be added to █ administration of omalizumab.

² Katelaris, C, et al. Omalizumab: recommendations for use in the Australasian context (A consensus paper of The Thoracic Society of Australia and New Zealand). April 2009. Found at: [www.thoracic.org.au/clinical-documents/command/download_file/id/44/filename/Omalizumab_\(Xolair\)_Recommendations_for_use_in_the_Australian_co](http://www.thoracic.org.au/clinical-documents/command/download_file/id/44/filename/Omalizumab_(Xolair)_Recommendations_for_use_in_the_Australian_context,_April_2009_A_consensus_paper_of_the_Thoracic_Society_of_Australia_and_Newzland.pdf) ntext,_April_2009_A_consensus_paper_of_the_Thoracic_Society_of_Australia_and_Newzland.pdf

6.22 Table 5 presents the additional resource utilisation associated with increased administration and monitoring costs applicable for the cost-minimisation analysis.

Table 5: Additional omalizumab costs incorporated into the cost-minimisation analysis

	Unit cost	Mepolizumab	Omalizumab	
		4-weekly	4-weekly	2-weekly
% patients		100%	█%	█%
Utilisation per year				
Administration				
Specialist (MBS 116)	\$75.50	█	█	█
General Practitioner (MBS 23)	\$37.05			
Nurse administration (MBS 82200)	\$8.20			█
Additional resources for anaphylaxis				
Adrenaline syringe (PBS 3409K/8698T)	\$96.43	█	█*	█*
Supervision post dose ≥ 20 min nurse attendance (MBS 82210)	\$33.80	█	█	█

Source: Tables 10-12 pp15-16, and Tables 14-16, p18 of the resubmission
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme
* One syringe every █, based on the approximate shelf-life of the syringe

6.23 The cost-minimisation analysis for mepolizumab, incorporating the full cost of omalizumab treatment, administration and monitoring, is presented in Table 6.

Table 6: Cost minimisation analysis for mepolizumab with omalizumab

	Mepolizumab	Omalizumab		Incremental weighted Cost
	4-weekly	4-weekly	2-weekly	
% patients	100%	█%	█%	
Omalizumab cost (AEMP)			\$█	
Administration				
Administration	\$23.01	\$█	\$█	\$█
Additional resources for anaphylaxis				
Adrenaline syringes	\$0	\$█	\$█	\$█
Supervision post dose	\$0	\$█	\$█	\$█
Total	\$23.01	\$█	\$█	\$█
Total, including drug cost			\$█	
Mepolizumab 100 mg cost				
Public hospital	\$█ ^a			
Private hospital	\$█			

Source: Tables 18-19, p20 of the resubmission
AEMP = approved ex-manufacturer price
^a \$█ + \$█

6.24 The proposed comparative cost-minimised price of mepolizumab relative to omalizumab reflected the full cost of treatment including drug, administration and monitoring costs.

Drug cost/patient/year: \$█.

6.25 The proposed cost of mepolizumab was \$█ per patient per four weeks, and \$█ per patient per year. (The estimated cost was based on the assumption that, as per omalizumab public and private hospital prescribing in 2014, 78.8% of patients would receive mepolizumab in the public hospital setting.) Mepolizumab is given

This was because the cohort of patients with eosinophils ≥ 300 cells/mL included patients who were eligible for:

- both mepolizumab and omalizumab, (mepolizumab would replace omalizumab); and
- mepolizumab only (mepolizumab replaces no treatment/standard of care).

Table 7: Net cost of mepolizumab to the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Mepolizumab patients					
Initiating mepolizumab	█	█	█	█	█
Meeting continuation criteria	█	█	█	█	█
Mepolizumab dispensings					
Prescriptions per year	█	█	█	█	█
Omalizumab substitution					
Patients treated per year	█	█	█	█	█
Packs of omalizumab substituted					
75 mg	█	█	█	█	█
150 mg	█	█	█	█	█
Cost of mepolizumab to PBS/RPBS					
Cost to PBS/RPBS ^a	\$ █	\$ █	\$ █	\$ █	\$ █
Cost offset of omalizumab to PBS/RPBS					
Cost offsets ^a	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █
Net cost of mepolizumab to PBS/RPBS					
Net cost to PBS/RPBS ^a	\$ █	\$ █	\$ █	\$ █	\$ █

Source: Table 20, p22 of the resubmission; and E_MEPO budget impact workbook_22.04.2016.xlsx

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Costs adjusted for co-payment

6.32 The minor resubmission estimated a net cost to the PBS/RPBS of less than \$10 million in Year 5 of listing, with a total net cost to the PBS/RPBS of \$10-\$20million over the first 5 years of listing. This is based on the published price of omalizumab.

6.33 The estimated net cost of mepolizumab to the MBS is summarised in Table 8. The resubmission incorrectly calculated that █% of omalizumab patients received two-weekly dosing, with █% receiving four-weekly dosing; however, the differences were negligible, compared to █% and █% for the economic evaluation.

Table 8: Net cost of mepolizumab to the MBS

	Year 1	Year 2	Year 3	Year 4	Year 5
Mepolizumab patients					
Initiating mepolizumab	█	█	█	█	█
Meeting continuation criteria	█	█	█	█	█
Cost of mepolizumab administration	\$ █	\$ █	\$ █	\$ █	\$ █
Omalizumab substitution					
Patients treated per year	█	█	█	█	█
Patients with 2-weekly dosing	█%	█%	█%	█%	█%
Patients with 4-weekly dosing	█%	█%	█%	█%	█%
Incremental use of MBS items					
Specialist: MBS item 116 (\$75.60)	█	█	█	█	█
GP: MBS item 105 (\$37.05)	█	█	█	█	█
Nurse admin: MBS item 82200 (\$8.20)	█	█	█	█	█
Nurse monitoring: MBS item 82210 (\$33.80)	█	█	█	█	█
Cost of omalizumab administration	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █

	Year 1	Year 2	Year 3	Year 4	Year 5
Cost to MBS					
Net cost of mepolizumab to MBS	-\$	-\$	-\$	\$	-\$

Source: Table 21, p22 of the resubmission; and E_MEPO budget impact workbook_22.04.2016.xlsx
 GP = general practitioner; MBS = Medicare Benefits Schedule

The redacted table shows that at year 5, the estimated number of patients initiating mepolizumab and meeting continuation criteria was less than 10,000 and the net save to the MBS would be less than \$10 million.

- 6.34 The minor resubmission estimated a net save to the MBS of less than \$10 million in Year 5 of listing, with a total net save to the MBS of less than \$10 million over the first 5 years of listing. The PBAC noted the Department's advice that some of these offsets would not be able to be claimed in the financial estimates that go to Government.
- 6.35 The overall net cost to the government health budget is summarised in Table 9.

Table 9: Net cost of mepolizumab to government health budget

	Year 1	Year 2	Year 3	Year 4	Year 5
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Net cost to MBS	-\$	-\$	-\$	\$	-\$
Overall net cost to government	\$	\$	\$	\$	\$

Source: Table 22, p22 of the resubmission; and E_MEPO budget impact workbook_22.04.2016.xlsx
 MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

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

- 6.36 The minor resubmission estimated a net cost to the government health budget of less than \$10 million in Year 5 of listing, with a total net cost of \$10 - \$20 million over the first 5 years of listing.

Financial Management – Risk Sharing Arrangements

- 6.37 The Sponsor indicated that it would request a Special Price Arrangement during price negotiations, should mepolizumab receive a positive recommendation from the PBAC.

7 PBAC Outcome

- 7.1 The PBAC recommended the Section 100 Highly Specialised Drugs Program (HSD) listing of mepolizumab for the treatment of severe eosinophilic asthma in patients aged 12 years and over.
- 7.2 The PBAC recommended the listing of mepolizumab on a cost-minimisation basis with omalizumab. The PBAC noted that the minor resubmission and sponsor's pre-PBAC response presented arguments for incorporating utilisation data into the calculation of equi-effective doses, but maintained their previous view that the equi-

effective doses should be derived from clinical trial data. The equi-effective doses accepted by PBAC were mepolizumab 100 mg and omalizumab 398 mg.

- 7.3 The PBAC noted that the minor resubmission's cost minimisation analysis incorporated cost-offsets to account for costs associated with administration, the treatment of adverse events (anaphylaxis), and longer supervision due to the potential of anaphylaxis with omalizumab. The PBAC agreed these offsets were reasonable.
- 7.4 The PBAC noted that the proposed restriction had been modified from the previous submission to make the listing more consistent with omalizumab, and considered that this was appropriate.
- 7.5 The clinical evidence in the minor resubmission remained unchanged from the March 2016 submission. The PBAC recalled that they had previously considered that the claims of non-inferior comparative effectiveness and safety of mepolizumab versus omalizumab were reasonable.
- 7.6 The PBAC noted that the estimated financial implications had been updated in the minor resubmission compared to the previous submission. The budget impact incorporated DUSC revisions and the updated costs associated with omalizumab administration and monitoring. The PBAC considered that this was appropriate.
- 7.7 The PBAC recommended that mepolizumab should not be treated as interchangeable with any other drugs
- 7.8 The PBAC advised that Section 100 medicines are currently considered out of scope for prescribing by nurse practitioners.
- 7.9 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 mepolizumab.
- 7.10 The PBAC noted that this submission is not eligible for an Independent Review because it has received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item. Restriction to be finalised. As far as appropriate should be aligned with omalizumab.

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

GSK welcomes the PBAC recommendation to list mepolizumab on the PBS for the treatment of severe eosinophilic asthma. Mepolizumab is the first anti-IL5 targeted biologic for the treatment of eosinophilic asthma.