6.11 MEPOLIZUMAB
Powder for injection 100 mg
Nucala®, GlaxoSmithKline Australia Pty Ltd

1 Purpose of Application

1.1 The minor submission requested changing the current PBS restriction for mepolizumab to remove the six month treatment break when switching from omalizumab to mepolizumab.

2 Requested listing

2.1 The submission requested the following changes to the restriction. Abridged versions of the mepolizumab restrictions are presented below. Changes proposed by the submission are shown in **bold;** additions proposed by the submission are added in italics and deletions are crossed out with strikethrough. Parts of the restriction that would require amendment associated with the proposed changes, as identified by the Secretariat, are shaded grey. Note that an abridged restriction is provided for continuing therapy with only the relevant sections included.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
MEPOLIZUMAB 100 mg injection, 1 vial	1	7	Public: $1638.00 Private: $1685.15	Nucala	GlaxoSmithKline Australia Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program- public and private
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Uncontrolled severe eosinophilic asthma
Treatment phase:	Initial treatment
Restriction Level / Method:	☒Authority Required - In Writing
Treatment criteria:	As per existing restriction (no changes proposed)
Clinical criteria:	Patient must be under the 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: (i) forced expiratory volume (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 micrograms), or (ii) airway hyperresponsiveness 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) peak expiratory flow (PEF) variability of greater than 15% between the two highest and two lowest peak expiratory flow rates during 14 days,

	AND 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 greater than or equal to 300 cells per microlitre in the last 12 months, AND Patient must have signed a patient or parent/guardian 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 The treatment must not be used in combination with~~, or within 6 months of treatment with,~~ PBS-subsidised omalizumab.
Population criteria:	As per existing restriction (no changes proposed)
Prescriber Instructions	Optimised asthma therapy includes: (i) Adherence to maximal inhaled therapy, including high dose inhaled corticosteroid (ICS) plus long-acting beta-2 agonist (LABA) therapy for at least 12 months, unless contraindicated or not tolerated; AND (ii) treatment with oral corticosteroids, either daily oral corticosteroids for at least 6 weeks, OR a cumulative dose of oral corticosteroids of at least 500 mg prednisolone equivalent in the previous 12 months, unless contraindicated or not tolerated. If the requirement for treatment with optimised asthma therapy cannot be met because of contraindications according to the relevant TGA-approved Product Information and/or intolerances of a severity necessitating permanent treatment withdrawal, details of the contraindication and/or intolerance must be provided in the Authority application. The following initiation criteria indicate failure to achieve adequate control and must be demonstrated in all patients at the time of the application: (a) an Asthma Control Questionnaire (ACQ-5) score of at least 2.0, as assessed in the previous month, AND (b) while receiving optimised asthma therapy in the past 12 months, experienced at least 1 admission to hospital for a severe asthma exacerbation, OR 1 severe asthma exacerbation, requiring documented use of systemic corticosteroids (oral corticosteroids initiated or increased for at least 3 days, or parenteral corticosteroids) prescribed/supervised by a physician. The Asthma Control Questionnaire (5 item version) assessment of the patient must be made at time of application for treatment (to establish baseline score) and again around 26 to 30 weeks after the first dose so that there is adequate time for a response to be demonstrated and for the application for continuing therapy to be processed. This assessment at around 26 to 30 weeks, which will be used to determine eligibility for continuing treatment, must be submitted within 4 weeks of the date of assessment, and no later than 2 weeks prior to the patient completing their current treatment course, to avoid an

	interruption to supply. Where a response assessment is not undertaken and submitted within this timeframe, the patient will be deemed to have failed to respond to treatment with mepolizumab. A patient who fails to respond to a course of PBS-subsidised mepolizumab for the treatment of uncontrolled severe eosinophilic asthma will not be eligible to receive further PBS-subsidised treatment with mepolizumab ~~or omalizumab~~ within 6 months of the date on which treatment was ceased. At the time of the authority application, medical practitioners should request 7 repeats to provide for an initial course of mepolizumab sufficient for 32 weeks of therapy. Mepolizumab and omalizumab may not be used concurrently ~~or within 6 months of each other.~~ A patient is required to have ceased treatment with omalizumab ~~for 6 months~~ prior to initiating treatment with mepolizumab.
Administrative Advice	As per existing restriction (no changes proposed)
Note (abridged)	**TREATMENT OF ADULT AND ADOLESCENT PATIENTS WITH UNCONTROLLED SEVERE EOSINOPHILIC ASTHMA** Patients are eligible to commence a 'mepolizumab treatment cycle' (initial treatment course with or without continuing treatment course/s) if they satisfy the eligibility criteria as detailed under the initial treatment restriction. Once a patient has either failed to achieve or maintain a response to mepolizumab, they are deemed to have completed a treatment cycle and they must have, at a minimum, a 6 month break in PBS-subsidised mepolizumab therapy before they are eligible to commence the next mepolizumab treatment cycle, or if eligible, an 'omalizumab treatment cycle'. The length of a treatment break is measured from the date the most recent treatment with PBS-subsidised mepolizumab is stopped to the date of the first application for initial treatment with mepolizumab under the new treatment cycle. There is no limit to the number of treatment cycles a patient may undertake in their lifetime. (1) How to prescribe PBS-subsidised mepolizumab therapy: (a) Initial treatment: Applications for initial treatment should be made where: i) A patient has received no prior PBS-subsidised mepolizumab treatment and wishes to commence such therapy; or ii) A patient wishes to recommence treatment with mepolizumab following a break in PBS-subsidised therapy of more than 6 months; or iii) A patient has received prior PBS-subsidised omalizumab and wishes to commence treatment with mepolizumab after a treatment break of 6 months. All applications for initial treatment for non-grandfather patients will be limited to provide for a maximum of 32 weeks of therapy for mepolizumab. <<(2) unchanged>> (3) Re-commencement of treatment after a 6 month break in PBS-subsidised therapy: A patient who wishes to trial a second or subsequent mepolizumab treatment cycle, or an initial omalizumab treatment cycle, following a break in PBS-subsidised therapy of at least 6 months, must re-qualify for initial treatment with respect to the indices of disease severity (oral corticosteroid dose, Asthma Control Questionnaire (ACQ-5) score, and relevant exacerbation history). Patients must have received optimised standard therapy, at adequate doses and for the minimum period specified, immediately prior to the time the new baseline assessments are performed.

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Treatment phase:	Continuing treatment
Treatment criteria:	As per existing restriction (no changes proposed)
Clinical criteria:	Patient must have demonstrated or sustained an adequate response to PBS-subsidised treatment with this drug, AND The treatment must not be used in combination with~~, or within 6 months of treatment with,~~ PBS-subsidised omalizumab.
Population criteria:	As per existing restriction (no changes proposed)
Prescriber Instructions	A patient who fails to respond to a course of PBS-subsidised mepolizumab for the treatment of uncontrolled severe eosinophilic asthma will not be eligible to receive further PBS-subsidised treatment with mepolizumab for this condition within 6 months of the date on which treatment was ceased.
Administrative Advice	As per existing restriction (no changes proposed)

3 Background

3.1 There are currently two biologics that are PBS-listed for uncontrolled severe asthma: mepolizumab, which targets the interleukin-5 pathway (i.e. eosinophil-mediated inflammation); and omalizumab which targets the immunoglobulin E pathway (i.e. allergic asthma). Eosinophilic and allergic asthma overlap in some patients; the submission stated that approximately 78% of patients who are eligible for omalizumab are also eligible for mepolizumab.

3.2 Mepolizumab was PBS listed on 1 January 2017 for the treatment of uncontrolled severe eosinophilic asthma in patients aged 12 years and over, as a Section 100 (Highly Specialised Drugs Program) written authority. It was recommended by the PBAC at its July 2016 meeting on a cost-minimisation basis with omalizumab.

3.3 At its November 2017 meeting, in its consideration of a minor submission for mepolizumab, the PBAC recommended extending the period of validity for the eosinophil blood test to 12 months to align with the current IgE test validity period for omalizumab.

3.4 Omalizumab was first recommended for listing in November 2010 and is currently PBS-listed for the treatment of patients aged six years and over with uncontrolled severe allergic asthma who have a total serum immunoglobulin E ≥ 30 IU/mL. It was recommended on a cost-effectiveness basis compared with standard of care.

3.5 The March 2018 PBAC also considered: a major submission seeking PBS-listing of benralizumab, a biologic for uncontrolled severe eosinophilic asthma (Item 5.01);

and a minor submission for benralizumab requesting changes to the current restrictions for biologics in uncontrolled severe eosinophilic asthma (Item 6.16).

4 Basis for requested restriction changes

4.1 The submission proposed removal of the requirement for patients with inadequate response to omalizumab to have a six month treatment interval between ceasing omalizumab and commencing mepolizumab. The PBAC noted that the treatment interval applies regardless of the reason for switching, including if the switch is due to adverse events, allergies or partial responsiveness.

Basis for six month treatment break: re-trial of same biologic

4.2 The PBAC noted that the six month treatment break was originally based on the omalizumab restriction, and related to re-trial of omalizumab in patients with inadequate response. Omalizumab was the first biologic listed for uncontrolled severe asthma, and included the requirement that "A patient who fails to respond to a course of PBS-subsidised omalizumab for the treatment of uncontrolled severe allergic asthma will not be eligible to receive further PBS-subsidised treatment with omalizumab for this condition within 6 months of the date on which treatment was ceased."

4.3 The March 2016 submission for PBS-listing of mepolizumab proposed a similar six-month break between re-trial of mepolizumab in patients with inadequate response (i.e. a six-month break in PBS-subsidised mepolizumab for patients who had either failed to achieve or maintain a response to mepolizumab).

Switching between different biologics

4.4 Additionally, the restriction that was proposed in the March 2016 submission would have allowed initiation of mepolizumab treatment after a 130 day (4.3 month) washout period for patients who had failed to respond to omalizumab treatment (i.e. a 130 day treatment break when switching between different biologics). The PBAC noted that it subsequently recommended a six month interval be included in the final restriction for consistency with the interval between re-trial of the same biologic agent (per the omalizumab restriction).

4.5 The PBAC noted that the 130 day treatment break originally proposed was based on the key mepolizumab clinical trials from the March and July 2016 submissions (comparing mepolizumab with placebo). The key trials included MENSA (588) and SIRIUS (575). In both trials, patients were excluded if they had received omalizumab within 130 days of Visit 1, or other monoclonal antibodies (to treat inflammatory disease) within five half-lives of Visit 1.

4.6 The PBAC noted that the half-lives of the biologics used to treat asthma are:

- benralizumab has an elimination half-life of 15 days (source: Benralizumab Product Information from the United States);
- mepolizumab has an elimination half-life of 16 to 22 days (source: page 3,

Mepolizumab Product Information); and

- omalizumab has an elimination half-life of 22 days (± 8 days). The Omalizumab Product Information states: "Omalizumab has a long serum half-life (mean 22 + 8.2 days). The long half-life is characteristic of IgG class immunoglobulins and a result of IgG recycling via its salvage receptor (FcRn). At the doses recommended for therapeutic use, average clearance is expected to represent dominantly IgG clearance and to be relatively slow (2.27-4.12 mL/kg/day)" (source: page 3, Omalizumab Product Information).

4.7 Thus, these medications would not be expected to be eliminated from the body until 75 to 110 days (2.5 to 4 months) after the last injection, based on clearance requiring five elimination half-lives.

4.8 The submission requested removal of the six month treatment break only for patients switching from omalizumab to mepolizumab. The submission stated that removal of the six month treatment break when switching between other biologics (or from mepolizumab to omalizumab) was not proposed because the evidence presented (the OSMO study) was specific to patients who had directly switched from omalizumab to mepolizumab. It further stated the evidence was not applicable to other agents that target the interleukin-5 (IL-5) pathway through different mechanisms, such as benralizumab.

4.9 The PBAC noted that the three biologic agents have different modes of action. Mepolizumab and benralizumab both target the IL-5 pathway (i.e. eosinophil-mediated inflammation). Benralizumab is an IL-5 receptor α antagonist, while mepolizumab targets the IL-5 ligand. On the other hand, omalizumab targets the immunoglobulin E pathway (allergic asthma).

Re-trial of the same agent and number of treatment breaks

4.10 The submission did not request changes to the six-month treatment break between re-trial of mepolizumab in patients who had either failed to achieve or maintain a response to mepolizumab.

4.11 The PBAC noted that there is currently no limit to the number of times that a patient can re-trial the same biologic agent following previous inadequate response. In other conditions, patients cannot keep re-using a biologic that they have previously failed to respond to. For example biologics for chronic plaque psoriasis include the clinical criteria: "patient must not have failed, or ceased to respond to, PBS-subsidised therapy with this drug for the treatment of this condition in the current Treatment Cycle".

4.12 The PBAC considered that the period of time between re-trial of biologics and the time for switching biologics may differ, and so would need to be reflected separately in the restrictions.

Separate initial restriction for patients switching between biologics

4.13 The current initial restriction requires patients to have:

- an Asthma Control Questionnaire (ACQ-5) score of at least 2.0, as assessed in the previous month;
- experienced a severe asthma exacerbation requiring either a hospital admission or use of systemic corticosteroids in the past 12 months;
- forced expiratory volume (FEV1) ≤ 80% predicted in the previous 12 months; and
- failed to achieve adequate control with optimised asthma therapy, which includes treatment with oral corticosteroids (doses specified).

4.14 The PBAC considered that these requirements may not be appropriate for patients who are switching to a new biologic, rather than first initiating biologic therapy. That is, the PBAC noted that patients may experience an inadequate response to a biologic (i.e. not achieve either (a) reduction in ACQ-5 score ≥ 0.5 from baseline, or (b) maintenance oral corticosteroid dose reduced by ≥ 25% from baseline, and no deterioration in ACQ-5 score from baseline), but may still not meet the initial restriction criteria outlined above. The PBAC noted that without a separate "initial" restriction for patients who are switching from a different biologic, there may be additional barriers to patients switching from one biologic to another.

4.15 The pre-PBAC response proposed that two separate mepolizumab initiation restrictions be developed:

- Initial treatment 1: new patient or patient recommencing treatment after a break of more than 6 months; and
- Initial treatment 2: patient must have already received omalizumab for severe asthma. The pre-PBAC response intended that this would enable direct switching from omalizumab to mepolizumab, without the requirement for patients to re-qualify under the baseline criteria.

4.16 The pre-PBAC response stated that issues relating to re-trial of the same biologic agent, the number of treatment breaks and cycling of biologic agents was beyond the scope of the submission. However, the PBAC considered that removal of the treatment break would require consideration of issues such as whether there should be limits on the number of times that a patient can use each agent, and the criteria for switching to an alternative biologic therapy. The PBAC considered that these issues were inter-related with re-trialling and cycling of biologics.

For more detail on PBAC's view, see section 6 PBAC Outcome.

5 Consideration of the evidence

Sponsor hearing

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

Consumer comments

5.2 The PBAC noted and welcomed the input from an organisation, the Centre of

Research Excellence in Severe Asthma (which included comment from the principal investigators from the Australian Mepolizumab Registry) via the Consumer Comments facility on the PBS website. Input was also provided from health care professionals (3) as part of the pre-PBAC response, and further general input relating to the restrictions for biologics in asthma was provided by from the Thoracic Society of Australia and New Zealand. The comments described the potential risks associated with a six month treatment interval in patients with severe asthma, such as an increased risk of asthma exacerbations, or increased requirements for oral corticosteroids, with a corresponding increase in the risk of adverse events.

5.3 The clinician comments outlined that the current six month interval when switching between different biologics may discourage clinicians from trialling an alternative biologic, even when switching may be clinically appropriate, for example due to partial effectiveness, adverse events (including anaphylaxis with omalizumab), or the eosinophilic/allergic features of the patient's asthma.

5.4 The PBAC noted that the the Thoracic Society of Australia and New Zealand and the Centre of Research Excellence in Severe Asthma both proposed changing the six month interval between different biologics. The organisations proposed that the requirement be either removed or replaced with an interval of one or two months. The PBAC further noted that the Centre of Research Excellence in Severe Asthma also proposed numerous other changes to the restriction.

Clinical studies

5.5 The minor submission stated that results of the OSMO study demonstrated the safety and efficacy of a direct switch from omalizumab to mepolizumab.

5.6 OSMO was a 32 week single-arm study in patients with severe eosinophilic asthma who were not optimally controlled with current omalizumab treatment. Patients were switched directly from omalizumab to mepolizumab without a washout period.

5.7 No Clinical Study Reports or publications from the OSMO study were provided with the submission, nor were these publicly available. While the Clinical Study Report was provided with the pre-PBAC response, the results were not verified as it was a minor submission.

Table 1: Studies presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Study number 204471 OSMO	A multi-centre, open label, single arm, 32-week treatment study in subjects with severe eosinophilic asthma not optimally controlled with current omalizumab treatment who are switched from omalizumab to mepolizumab 100mg subcutaneous	N/A

Source: Minor submission, pg.9

5.8 The submission stated that the OSMO study included a one to four week run-in period during which patients remained on current treatment, including omalizumab. At the end of the run-in period, patients commenced treatment with mepolizumab (100 mg sub-cutaneous every four weeks). No washout period was used:

mepolizumab was commenced one to five weeks after the last dose of omalizumab (depending on whether the patient was on the every two–weekly or four-weekly omalizumab dosing regimen). Patients continued to receive mepolizumab every four weeks for the 32 week study duration.

5.9 Per the study's inclusion criteria, patients were required to have:

- at least four months of omalizumab treatment prior to Visit 1;
- regular high-dose inhaled corticosteroids in the prior 12 months;
- ≥ 2 exacerbations requiring treatment with systemic corticosteroids in the prior 12 months;
- blood eosinophil count of at least 300 cells/µL in the last 12 months, or at 150 cells/µL at the start of the trial; and
- ACQ-5 score of ≥1.5 at the start of the trial.

5.10 The submission stated the inclusion criteria were representative of the current PBS restriction for mepolizumab initiation treatment with respect to prior exacerbations, corticosteroid use and eosinophil levels. However, the PBS criteria require an ACQ-5 score of ≥ 2 at initiation (i.e. the PBS criteria require patients to have a poorer level of asthma control). The Pre-PBAC response stated that the mean ACQ-5 score at baseline in the OSMO study was 3.19 (standard deviation: 0.94).

5.11 The primary endpoint of the OSMO study was mean change from baseline in ACQ-5 score at Week 32, and the secondary endpoints included the frequency of clinically significant asthma exacerbations.

5.12 145 patients received at least one dose of mepolizumab and were included in the intention to treat (ITT) population. The median duration of prior treatment with omalizumab was 30 months (range: 4 to 161 months). At baseline, the mean age of patients included in OSMO was 54 years (standard deviation: 14 years), 24% of patients were on regular maintenance oral corticosteroids and the mean number of exacerbations in the previous year was 3.3.

Comparative effectiveness

Change in ACQ-5 score from baseline

5.13 The OSMO study found that patients treated with mepolizumab (after a direct switch from omalizumab) experienced an improvement in ACQ-5 score, with a mean change from baseline of -1.45 (standard error: 0.01) at Week 32. The submission stated that 77% of patients (111/145) reported an improvement in ACQ-5 score of at least 0.5 points. As the OSMO study was open label, and the ACQ-5 questionnaire was completed and scored by patients, results of the change in ACQ-5 score had a moderate-to-high risk of bias. Further, the comparison was versus patients who were poorly controlled at baseline.

5.14 As the OSMO study did not include a comparator arm, the submission performed a number of naïve indirect comparisons which compared the results from OSMO with the results of the double-blind placebo controlled trials that were used in the March and July 2016 mepolizumab submissions, which compared mepolizumab with placebo (MENSA, MUSCA and DREAM). These trials generally excluded patients who had received omalizumab within 130 days prior to study enrolment. The submission presented naïve indirect comparisons versus:

- the individual arms of the MENSA and MUSCA trials, and
- meta-analyses of placebo arms. Two meta-analyses were conducted:
  - "Historical placebo effect 1" was based on a meta-analysis of the placebo arms of MENSA and DREAM at Week 32;
  - "Historical placebo effect 2" was based on a meta-analysis of the placebo arms of MENSA and MUSCA in patients with prior omalizumab use.

5.15 The results of these analyses are presented in Table 2.

Table 2: Previous ACQ-5 improvements from baseline from double-blind phase III studies

			Mepolizumab	Placebo	
			LS mean change (SE)		
OSMO versus results of previous randomised clinical trials of mepolizumab vs placebo					
OSMO (Week 32)			-1.45	N/A	
Previous randomised trials of mepolizumab versus placebo					
MENSA (Week 32): Overall			-0.94	-0.50	
MENSA (Week 32): Previous omalizumab subgroup			-1.16	-0.29	
MUSCA Week 24			-0.80	-0.40	
OSMO versus meta-analyses of placebo arms					
	ACQ-5: Baseline LS mean (SE)	**ACQ-5: 32-week LS mean (SE)**	**Mepolizumab**	**Placebo**	**Naïve indirect comparison**
OSMO (32 weeks)	3.20 (0.076)	1.75 (0.096)	-1.45 (0.107)		
Historical placebo 1				-0.55 (0.05)	-0.90 (-1.13, -0.66)
Historical placebo 2				-0.11 (0.14)	-1.34 (-1.68, -1.00)

Source: Tables 4 and 5, minor submission, pp.12-13; The results from the DREAM trial were not presented as it included an unregistered dose of mepolizumab.

5.16 The submission stated the improvement in ACQ-5 score from baseline was consistent with improvements seen in the randomised, double-blind, placebo-controlled trials, MENSA and MUSCA. Further, the submission stated that the OSMO study found a statistically significant improvement in ACQ-5 score when compared with the historical placebo effects meta-analyses.

Clinically significant asthma exacerbations

5.17 As shown in Table 3, the submission stated that the rate of clinically significant exacerbations was reduced by 64% compared with the 12 months prior to screening (rate ratio 0.36 (95% confidence interval 0.28, 0.14). The pre-PBAC response outlined

that a patient's rate of exacerbations prior to screening were confirmed through medical or pharmacy records.

5.18 The submission also compared the results with those observed in the double-blind placebo controlled trials that had formed the basis of its March and July 2016 submissions (as shown in Table 3).

Table 3: Exacerbations rates (ITT population)

	Mepolizumab	Pre-mepolizumab	Rate ratio (95% CI) On vs off mepolizumab		
OSMO study (n = 145)					
Clinically significant exacerbations					
Exacerbation rate/year	1.18	3.26	0.36 (0.28, 0.47)		
Exacerbations requiring an ER visit or hospitalisation					
Exacerbation rate/year	0.19	0.63	0.31 (0.18, 0.53)		
Exacerbations requiring hospitalisation					
Exacerbation rate/year	0.12	0.17	0.74 (0.40, 1.37)		
Naïve comparison with previous studies: rate of clinically significant exacerbations					
	Mepolizumab			**Placebo**	**Rate ratio Mepolizumab vs placebo**
MENSA (Week 32): Overall	0.83			1.74	0.47
MENSA (Week 32): Previous omalizumab subgroup	1.00			2.33	0.43
MUSCA Week 24	0.51			1.21	0.42

Source: Table 6 and 7, pp 13-14 of the minor submission

5.19 The submission stated that the reduction in the rate of clinically significant exacerbations observed in OSMO was consistent with the reduction seen in randomised placebo-controlled trials of mepolizumab (MENSA and MUSCA).

Comparative harms

5.20 The submission claimed that mepolizumab, when used following a direct switch from omalizumab (without a washout period), was well tolerated and that no new safety concerns were identified compared with the known safety profile of mepolizumab in severe eosinophilic asthma.

5.21 Table 4 below shows the reported adverse events and immunogenicity profile of mepolizumab from the OSMO study, compared with the aforementioned randomised placebo-controlled trials of mepolizumab.

Table 4: Adverse event and immunogenicity profile of mepolizumab 100 mg SC from previous phase III double-blind studies

N (%)	OSMO	MENSA		SIRIUS		MUSCA	
	MEPO (N = 145)	MEPO	PBO	MEPO	PBO	MEPO	PBO
Any AEs	124 (86%)	152 (78%)	158 (83%)	57 (83%)	61(92%)	192 (70%)	207 (74%)
Treatment-related AEs	33 (23%)	39 (20%)	30 (16%)	21 (30%)	12 (18%)	31 (11%)	25 (9%)
SAEs	16 (11%)	16 (8%)	27 (14%)	21 (30%)	18 (12%)	15 (5%)	22 (8%)
Withdrawals due to AEs	2 (1%)	1 (1%)	4 (2%)	3 (4%)	3 (5%)	2 (< 1%)	3 (1%)
Deaths	0	0	1 (1%)	0	1 (2%)	0	0
Most common AEs (≥10%)	Headache (28%), URTI (17%), bronchitis (13%), arthralgia (10%), fatigue (10%)	Asthma worsening, nasopharyngitis, headache, URTI, bronchitis, sinusitis, fatigue				Headache, nasopharyngitis	
Injection-site reactions	5 (3%)	17 (9%)	6 (3%)	4 (6%)	2 (3%)	7 (3%)	6 (2%)
Systemic hypersensitivity	1 (< 1%)	N/A		N/A		2 (< 1%)	2 (< 1%)
Anti-drug antibodies	11 (8%)	9 (5%)	4 (2%)	6 (4%)		10 (4%)	5 (2%)
Neutralising antibodies	0	0	0	1 (< 1%)		0	0

Source: Table 12, p16 of the Minor submission

5.22 The submission stated that 86% of patients reported an adverse event; 23% of patients reported an adverse event that was considered to be related to treatment. The submission stated that 11% of patients in OSMO reported serious adverse events, none of which were considered to be related to treatment.

5.23 The submission stated that 8% of patients in OSMO had anti-mepolizumab antibodies detected at any time post-baseline. This was higher than observed in other trials of mepolizumab. In OSMO, post-baseline samples were negative for neutralising antibodies.

5.24 The submission concluded that the safety and immunogenicity profile of mepolizumab in OSMO was consistent with the known safety profile observed in previous randomised placebo-controlled trials of mepolizumab (MENSA, SIRIUS, MUSCA).

5.25 The PBAC considered that the OSMO study demonstrated that mepolizumab, when used following a direct switch from omalizumab (without a washout period), was well tolerated, with a safety profile consistent with previous randomised placebo-controlled trials of mepolizumab.

Estimated PBS usage & financial implications

5.26 The submission stated that there would be no additional cost to the PBS/RPBS associated with the requested change to the restriction (removing the six-month treatment break between omalizumab and mepolizumab). The submission claimed

this was because mepolizumab was listed on a cost-minimisation basis with omalizumab.

5.27 The submission acknowledged that currently, during the six-month interval patients would be treated with corticosteroid therapy (which has a lower cost to the PBS) but that this would be offset by an increased risk of exacerbations (which are associated with increased GP and hospital costs). As such, the requested change may be associated with increased costs to the PBS/RPBS, for example due to increased mepolizumab drug costs during the six-month treatment break.

For more detail on PBAC's view, see section 6 PBAC Outcome.

6 PBAC Outcome

6.1 The PBAC deferred making a decision on the request to remove the six month treatment break when switching between different biologics for the treatment of uncontrolled severe eosinophilic asthma and uncontrolled severe allergic asthma. The PBAC considered that removal of the treatment break would have flow-on implications and would require consideration of issues around re-trialling of the same biologic, switching between and cycling of biologics in severe asthma. The deferral was to enable further consideration and broader discussion given the complexity of these matters.

6.2 The PBAC noted that there was support from a number of clinician groups for changes to the six-month treatment break when switching between different biologics in severe asthma. The comments highlighted the range of inter-related factors that would need to be taken into account if any change were made to this aspect of the restriction.

6.3 The PBAC noted that the OSMO study investigated the efficacy and safety of a direct switch from omalizumab to mepolizumab without a wash-out period. The PBAC considered that, based on the data provided, mepolizumab when used following a direct switch from omalizumab (without a washout period) had a safety profile consistent with previous randomised placebo-controlled trials of mepolizumab.

6.4 The PBAC noted the six month treatment break was originally based on the omalizumab restriction when it was the only biologic listed for asthma and the requirement initially only related to re-trialling omalizumab in patients with an inadequate response.

6.5 The PBAC noted that the treatment breaks when switching between different biologics were somewhat consistent with the exclusion criteria of the key trials of biologics in asthma. The PBAC noted that the original mepolizumab restriction that was proposed by the sponsor (in March 2017) requested a 130 day treatment break for patients who had failed to respond to omalizumab. This was based on the key mepolizumab trials, which excluded patients who had received omalizumab within 130 days of enrolment, or other monoclonal antibodies within five half-lives of enrolment. The PBAC noted that it subsequently recommended a six month

treatment break be included in the final restriction for consistency with the break between re-trial. In this context, the PBAC further noted the long elimination half-lives of the biologics for asthma (15 to 22 days).

6.6 The PBAC noted input from the Centre of Research Excellence in Severe Asthma and the Thoracic Society of Australia and New Zealand, which stated that patients may be at risk of severe exacerbations during treatment breaks. As such, the PBAC considered that the requirements warranted further review. The PBAC considered that any changes to the time periods between use of biologics should take into account the inter-related issues associated with re-trialling, switching and cycling of biologics in asthma, which are each discussed in turn below. Given the complexity, the PBAC considered that such matters would best be informed by broader discussion.

6.7 With respect to re-trialling of the same biologic, the PBAC considered that broader discussion was required as to:

- the circumstances under which it would be appropriate to re-trial the same biologic agent rather than trial other treatment options; and
- whether the same agent could be re-trialled following previous inadequate response. If so, consideration would be required as to how many times an agent could be re-trialled and the time period between re-trialling of the same agent.

6.8 With respect to switching between different biologics, the PBAC considered that broader discussion was required as to:

- the criteria for switching to an alternative biologic therapy;
- whether the six month break should be replaced with a break of a different duration. The PBAC noted that clinical organisations had proposed that the requirement be either removed or replaced with a treatment break of one or two months;
- whether there should be limits on the number of times that a patient can use each agent (refer to cycling between the biologics, discussed below); and
- whether a separate initial restriction would be required to enable patients to switch from one biologic to another without having to meet the current initial restriction requirements (i.e. separate initial restrictions may be required for: patients who are newly eligible for biologic therapy; and those who were previously eligible and now initiating a different biologic).

6.9 With respect to cycling between the biologics, the PBAC considered that broader discussion was required to inform on the number of agents that could be appropriate to use over a defined time period, including evidence supporting the clinical plausibility of cycling between agents. This could potentially include consideration of: a maximum number of biologics for the treatment of asthma over a certain timeframe (e.g. similar to the PBS arrangements for chronic plaque psoriasis, wherein patients with an inadequate response to three biologic agents must have a

minimum five year break before re-trialling biologics); or a maximum number of biologics for the treatment of asthma in a lifetime (e.g. similar to the PBS arrangements for rheumatoid arthritis, wherein patients can trial a maximum of five biologics within a life-time).

6.10 The PBAC considered that such changes to the PBS restrictions for the biological medicines for the treatment of severe asthma are likely to have implications for the total cost to the PBS of these medicines.

6.11 The PBAC noted that this submission is not eligible for an Independent Review, as listing is not requested for an entirely different disease, different subtype or different population or stage of the disease.

Outcome:

Deferred

7 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.

8 Sponsor's Comment

GSK welcomes the opportunity for a broader discussion with relevant stakeholders to help determine whether removal of the treatment break between ceasing omalizumab and commencing mepolizumab is appropriate. GSK recognises that a decision around this could have flow on implications for other biologics used to treat asthma.

In terms of the additional barriers to biologics use in asthma raised by the Committee and the Centre for Research Excellence for Severe Asthma, GSK believes that these are outside of the scope of this minor submission. However, GSK welcomes a separate broader discussion with relevant stakeholders regarding these.