5.09 MEPOLIZUMAB, Injection 100 mg in 1 mL pre-filled syringe, Injection 100 mg in 1 mL pre-filled pen, Nucala®, GlaxoSmithKline Australia Pty Ltd.

1 Purpose of Application

1.1 The minor submission sought a Section 100 (Highly Specialised Drugs Program) listing for new presentations of mepolizumab (Nucala Pen (pre-filled pen) and Nucala PFS (pre-filled syringe) from herein), for the treatment of uncontrolled severe eosinophilic asthma.

2 Background

Previous PBAC consideration

2.1 Mepolizumab (powder for injection; Nucala Vial from herein) was first considered by the PBAC at its March 2016 meeting and was recommended by the PBAC on a cost-minimisation basis with omalizumab in July 2016. Nucala Vial was PBS-listed on 1 January 2017.

Registration status

2.2 Nucala Pen and PFS were both TGA registered on 2 December 2019 with the same indication as Nucala Vial, as add-on treatment for severe eosinophilic asthma in patients aged 12 years and over.

2.3 The TGA Delegate determined that mepolizumab solution (contained in the Nucala Pen and PFS) was bio-analytically comparable to mepolizumab lyophilised powder (contained in Nucala Vial) for injection and were both administered subcutaneously at the same dose regimen (once every four weeks).

3 Requested listing

3.1 The submission requested the listing of Nucala Pen and PFS under the same conditions as the currently PBS-listed Nucala Vial.

3.2 Additionally, a grandfather restriction was proposed to allow patients to transition from an Early Access Program (EAP) to PBS-subsidised mepolizumab. The grandfather restriction aimed to mirror the current initial treatment restriction, with indices of disease severity being measured prior to commencement of non-PBS subsidised therapy. Patients accessing mepolizumab through the EAP will still be required to meet all response criteria prior to being approved for continuing treatment.

3.3 The minor submission estimated that [redacted] patients that will be enrolled in an EAP which will run from February to July 2020. The aim of the program is to help patients gain familiarity with the use of the new presentations of mepolizumab. The pre-PBAC response noted that at the time of writing (March 2020), the EAP was yet to commence and the estimated number of patients who would be enrolled would likely reduce due to the delay.

3.4 The minor submission requested that substitution at a pharmacy level ('a' flagging) between the three mepolizumab presentations not be permitted once listed.

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

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

Consumer comments

4.2 The PBAC noted and welcomed the input from 1 organisation via the Consumer Comments facility on the PBS website. Asthma Australia provided comments describing a range of benefits of having different device options for mepolizumab available. The comments noted that the new forms would be more convenient for patients as they can self-administer the new forms of mepolizumab at home in their own time rather than having to attend a clinic to be administered the vial. The new forms also reduced the likelihood of preparation error and contamination, resulting in more accurate and safer delivery of the medicine.

Clinical trials

4.3 The minor submission presented three clinical study reports (CSRs) and three full-text primary publications to demonstrate that the Nucala Pen and PFS were equivalent to the Nucala Vial. Details of the studies presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
CSR 204958 (GSK 2017a)	An open label, randomised, three arm, single dose, multicentre, parallel group study in healthy subjects to compare the pharmacokinetics of subcutaneous mepolizumab when delivered as a liquid drug product in a pre-filled syringe or an autoinjector with a reconstituted lyophilised drug product from a vial.	GSK Clinical Study Report 2017
Shabbir 2019 (Primary publication)	The pharmacokinetics and relative bioavailability of mepolizumab 100mg liquid formulation administered subcutaneously to healthy participants: a randomised trial.	Shabbir S., et al., Clin Pharmacol Drug Dev. 2019 Jul 17. doi: 10.1002/cpdd.726. [Epub ahead of print]

Trial ID	Protocol title/ Publication title	Publication citation
Non-randomised studies		
CSR 205667 (GSK 2017b)	An open-label, single arm, repeat dose, multi-centre study to evaluate the use of a pre-filled syringe for the subcutaneous administration of mepolizumab in subjects with severe eosinophilic asthma.	GSK Clinical Study Report 2017
CSR 204959 (GSK 2017d)	An open-label, single arm, repeat dose, multi-centre study to evaluate the use of an autoinjector for the subcutaneous administration of mepolizumab in subjects with severe eosinophilic asthma.	GSK Clinical Study Report 2017
Bel 2019 (Primary publication)	Usability of mepolizumab single-use pre-filled syringe for patient self-administration.	Bel EH., et al. Journal of Asthma 2019 Apr 24:1-10. doi: 10.1080/02770903.2019.1604745. [Epub ahead of print]
Bernstein 2019 (Primary publication)	Usability of mepolizumab single-use autoinjector for patient self-administration.	Bernstein D et al., J Asthma. 2019 Jun 28:1-12. doi: 10.1080/02770903.2019.1630641. [Epub ahead of print]

Source: Minor Submission, Table 8 (pp21).

4.4 Study 204958 was a randomised, single dose study looking at the administration of Nucala Pen or PFS compared to Nucala Vial which was delivered by a health care practitioner subcutaneously to 244 healthy patients. The primary outcome observed the pharmacokinetic (PK) parameters at least 8 hours after dosing, and followed up 85 days after dosing. The site of injection was randomised.

4.5 Study 204959 (Pen) and 205667 (PFS) were real-world studies primarily aimed to evaluate the ability of patients with severe eosinophilic asthma to self-administer three doses of Nucala Pen and PFS. Pharmacodynamic (PD) and PK comparability were other endpoints measured. Both studies were open-label, single-arm, multi-dose, multi-centre, 12-week studies. Study 204959 had 159, and study 205667 had 56 subjects. Study 204959 study involved Australian sites.

Comparative effectiveness

Study 204958

4.6 The results of Study 204958, as shown in the table below, demonstrated that the PK parameters were consistent across all three presentations, and the 90% confidence intervals for all three PK parameters were within the 80-125% range determined for claiming bioequivalence in PK effect.

Table 2: Statistical analysis of mepolizumab plasma PK parameters

PK Parameter	Test Treatment	Adjusted Geometric Mean (SE [logs])*		Ratio (Test/Reference)	90% CI for Ratio (Test/Reference)
		Test	MEPO Vial (Reference)		
Cmax (µg/mL)	MEPO Pre-filled pen	12.01 (0.028)	11.55 (0.027)	1.04	(0.98, 1.11)
	MEPO Pre-filled syringe	12.14 (0.027)	11.51 (0.027)	1.06	(0.99, 1.12)

PK Parameter	Test Treatment	Adjusted Geometric Mean (SE [logs])*		Ratio (Test/Reference)	90% CI for Ratio (Test/Reference)
AUC (0-∞) (day*µg/mL)	MEPO Pre-filled pen	478.94 (0.026)	449.70 (0.026)	1.07	(1.00, 1.13)
	MEPO Pre-filled syringe	457.03 (0.029)	447.92 (0.028)	1.02	(0.95, 1.09)
AUC (0-t) (day*µg/mL)	MEPO Pre-filled pen	435.46 (0.029)	403.00 (0.028)	1.08	(1.01, 1.15)
	MEPO Pre-filled syringe	417.93 (0.031)	401.30 (0.030)	1.04	(0.97, 1.12)

Source: Minor submission, Table 11 (pp24).
* Adjusted for injection site (arm, abdomen, thigh) and baseline weight (log_e scale); CI = confidence interval; MEPO = mepolizumab

4.7 The PK effect did not appear to differ markedly when different sites of injection (upper arm, abdomen or thigh) were used.

4.8 The PD effect (as determine by blood eosinophil count) was measured as a secondary outcome, and found to be similar across all three presentations.

Studies 204959 and 205667

4.9 Both studies showed a high injection success rate, with all but one subject being able to self-administer their Nucala Pen or PFS.

- Responses from a questionnaire revealed an overall positive experience from the subjects/caregivers regarding the usability of the PFS/pen.
- For patients who had been receiving treatment with Nucala Vial at screening, 96% showed a preference for receiving the Nucala Pen or PFS at home.
- The PK and PD results showed that mepolizumab plasma concentrations and blood eosinophil counts were consistent with those observed for Nucala Vial.

Comparative harms

4.10 The minor submission claimed that the results from Studies 204959 and 205667 demonstrated that the safety profiles of Nucala Pen and PFS are consistent with that of Nucala Vial and no new safety concerns were identified.

Clinical claim

4.11 The minor submission claimed Nucala Pen and PFS are non-inferior in terms of comparative efficacy and safety to Nucala Vial. The PBAC considered these claims reasonable.

Economic analysis

4.12 The minor submission presented a cost-minimisation analysis of Nucala Pen and PFS compared with Nucala Vial. Given Nucala Pen and PFS have the same dosage regimen as Nucala Vial, the equi-effective doses were estimated as one mepolizumab 100 mg pen (solution) or one mepolizumab 100 mg PFS (solution) and one mepolizumab 100 mg vial (powder for injection).

4.13 The minor submission proposed the ex-manufacturer price (AEMP) for Nucala Pen and PFS to be equivalent to Nucala Vial, and that the Special Pricing Arrangement (SPA) for Nucala Vial should apply to Nucala Pen and PFS.

Estimated PBS usage & financial implications

4.14 The minor submission used a market share approach to estimate the uptake and financial implications of Nucala Pen and PFS and the currently listed Nucala Vial. The minor submission assumed that Nucala Pen and PFS would substitute for 100% of Nucala Vial use within the first year of listing. The minor submission predicted no growth within the mepolizumab market nor the overall market for uncontrolled severe eosinophilic asthma as a result of listing the Pen and PFS forms. Therefore, the minor submission estimated there to be no net additional cost to the PBS over six years.

Table 3: Financial impact of MEPO pre-filled pen/pre-filled syringe over six years

	Year 1[a]	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated number of PBS/RPBS scripts for mepolizumab						
Total number of PBS/RPBS services	16,650	22,124	27,482	32,840	38,203	43,571
Estimated net cost to PBS/RPBS (effective DPMQ less co-payments)						
Net PBS/RPBS cost for Nucala Pen/PFS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net PBS/RPBS saving for Nucala Vial[b]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated net cost to MBS[c]						
Net cost to MBS for Nucala Pen/PFS	$53,893	$70,814	$87,178	$103,542	$119,922	$136,315
Net saving to MBS for Nucala Vial	$138,030	$183,633	$228,104	$272,575	$317,087	$361,639
Net financial implications						
Net cost PBS/RPBS	$0	$0	$0	$0	$0	$0
Net cost MBS	-$84,137	-$112,819	-$140,926	-$169,033	-$194,166	-$225,324
Net cost to Government	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**

a Year 1 represents financial year Jul 19-Jun 20

b Assuming 100% substitution with Nucala Pen/PFS

c Assuming 100% of administrations of Nucala Vial would be by a health care professional and 54% administrations of Nucala PFS/Pen would be by a health care professional in Year 1, reducing to 31% in Year 2 and beyond.

Source: Table 35 and 37 of minor submission; Electronic Attachment F MEPO_AI_PFS_utilisation_and_cost_model.xls

Abbreviations: PBS=pharmaceutical benefits scheme; RPBS= repatriation pharmaceutical benefits scheme.

4.15 The minor submission claimed that with the substitution of Nucala Pen and PFS for Nucala Vial would result in savings to the MBS, including an estimated $84,000 in Year 1 and up to a total of $926,000 over the first six years of listing due to the reduction in visits to a health care professional for administration of mepolizumab. The minor submission assumed that 54% of administrations of Nucala PFS and Pen would be by a health care professional in Year 1, reducing to 31% in Year 2 and beyond, compared with 100% for Nucala Vial.

4.16 The minor submission did not include the grandfathered patients in the financial estimates due to the assumption that they would not have any additional impact on the growth of the mepolizumab market, and they would have otherwise initiated Nucala Vial, or switched from another biological anyway, had the EAP not existed. The PBAC considered that it was not appropriate to exclude an estimate for grandfathered patients and that this should be explicitly included in the financial model.

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC recommended the listing of new forms of mepolizumab (pre-filled pen and pre-filled syringe; Nucala Pen and Nucala PFS respectively), on the basis that they should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program) for the treatment of uncontrolled severe eosinophilic

asthma. The PBAC considered that a form of mepolizumab that can be self-administered will provide a convenience benefit to some patients.

5.2 The PBAC recommended the listing of Nucala Pen and PFS on a cost-minimisation basis to mepolizumab powder for injection (Nucala Vial), with equi-effective doses being one mepolizumab 100 mg pen (solution) or one mepolizumab 100 mg PFS (solution) to one mepolizumab 100 mg vial (powder for injection).

5.3 The PBAC recommended that the restrictions for Nucala Pen and PFS should be consistent with those for Nucala Vial for the treatment of uncontrolled severe eosinophilic asthma.

5.4 The PBAC considered it was reasonable to include a grandfather restriction to allow patients enrolled in an Early Access Program (EAP) to transition onto PBS-subsidised treatment if eligible. The PBAC recommended the following regarding the grandfather listing:

- Patients must meet all the usual initial entry criteria that a non-grandfather patient would be expected to meet prior to having commenced non-PBS subsidised therapy;
- For patients who have received 28 weeks or more of therapy, an adequate response to treatment must be declared to have been achieved, consistent with the continuing treatment listing for non-grandfather patients;
- For patients yet to receive an adequate treatment duration up to the first 32 weeks, the grandfather listing is to provide the balance of 32 weeks of treatment;
- The listing be operational for a strict 6 months as this would be sufficient time for patients from the EAP to transition onto PBS-subsidised treatment.

5.5 The PBAC considered that Nucala Pen and PFS were non-inferior to Nucala Vial in terms of comparative efficacy and safety which was supported by the clinical evidence provided and the TGA Delegate's decision that both presentations were bio-analytically comparable to Nucala Vial.

5.6 The PBAC considered it was reasonable that Nucala Pen and PFS would substitute for Nucala Vial use and would result in a reduction in visits to a health care professional. The PBAC agreed with the submission that it was unlikely that the availability of the new forms would grow the mepolizumab market or the overall market for uncontrolled severe eosinophilic asthma. Therefore, the PBAC considered there should be no net additional cost to the PBS over six years.

5.7 The PBAC reaffirmed its March 2018 advice, under Section 101 (3BA) of the *National Health Act 1953*, that mepolizumab and benralizumab should be treated as interchangeable on an individual patient basis (paragraph 7.16, item 5.01 benralizumab, Public Summary Document (PSD), March 2018, PBAC meeting).

5.8 The PBAC advised, under Section 101 (4AACD) of the *National Health Act 1953*, that mepolizumab 100 mg in 1 mL pre-filled pen, mepolizumab 100 mg in 1 mL pre-filled

syringe and mepolizumab powder for injection 100 mg should not be considered equivalent for the purposes of substitution (i.e., 'a' flagged in the Schedule with a NOTE stating PBS of one form and PBS of another form are equivalent for the purposes of substitution). The PBAC noted the three forms had different injection techniques and there was a risk of incorrect injecting of a dose if patients are dispensed a different presentation to what they were trained to use.

5.9 The PBAC advised that mepolizumab is not suitable for prescribing by nurse practitioners.

5.10 The PBAC recommended that the Early Supply Rule should not apply.

5.11 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

6 Recommended listing

6.1 Add 2 new presentations (syringe and pen device) to the existing mepolizumab PBS listing.

6.2 Add a new grandfather listing for the 2 new presentations:

- Listing to be finalised

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

8 Sponsor's Comment

GSK welcomes the PBAC recommendation. This presentation of mepolizumab provides a welcome additional treatment option for Severe Eosinophilic Asthma patients. The ability to self-administered doses further empowers the patient with their disease management.