5.06 EPTINEZUMAB, Solution concentrate for I.V infusion 100 mg in 1 mL, Vyepti®, Lundbeck Australia Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested an Authority Required listing for eptinezumab for the treatment of chronic migraine (CM) in patients who have had an inadequate response, intolerance or contraindication to three or more prior prophylactic therapies for CM.

1.2 The basis for the submission was a claim of non-inferiority against galcanezumab (the main comparator) and fremanezumab (secondary comparator), supported by an indirect treatment comparison (ITC) using placebo as the common comparator. The submission presented a cost-minimisation approach (CMA) against galcanezumab. The key components of the clinical issue addressed by the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with chronic migraine who have experienced an inadequate response, intolerance or a contraindication to at least three preventative migraine medications
Intervention	Eptinezumab 100 mg administered by intravenous infusion every 12 weeks
Comparators	1. Galcanezumab 240 mg initially followed by 120 mg every month 2. Fremanezumab 225 mg every month
Outcomes	Reduction in number of monthly migraine headache days, improvement in 50% response rate
Clinical claims	Eptinezumab is non-inferior in terms of efficacy and safety when compared to galcanezumab and fremanezumab

Source: Table 12, p29 of the submission

2 Background

Registration status

2.1 Eptinezumab was listed on the Australian Register of Therapeutic Goods on 16 June 2021 for the preventive treatment of migraine in adults.

Previous PBAC consideration of treatments for chronic migraine

2.2 There are a range of treatments for CM available on the PBS currently subsided including botulinum toxin type A, galcanezumab and fremanezumab.

2.3 In July 2019, the PBAC recommended the Authority Required listing of galcanezumab for the treatment of CM in patients who have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications. In November 2020, the PBAC provided further advice regarding the cost minimisation

approach, financial estimates and risk sharing arrangement. Galcanezumab was listed on the PBS for CM on 1 June 2021.

2.4 In March 2020, the PBAC recommended the Authority Required listing of fremanezumab for the treatment of CM in patients who have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications. Fremanezumab was listed on the PBS for CM on 1 August 2021.

2.5 The PBAC previously considered fremanezumab non-inferior to galcanezumab in terms of effectiveness and safety and that the equi-effective doses were fremanezumab 225 mg every month and galcanezumab 240 mg initially followed by 120 mg every month (paragraph 5.11, galcanezumab Public Summary Document (PSD), November 2020).

2.6 In March 2022, the PBAC recommended amending the current PBS listing of galcanezumab for CM to include the treatment of patients with high frequency episodic migraine (EM) by removing the criteria for patients to have an average of 15 or more headache days per month.

2.7 Eptinezumab has not been considered by the PBAC previously.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, restriction, manner of administration, form	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Initial treatment				
Eptinezumab 100 mg IV infusion	1	0	Published Price $ [redacted] Effective Price: TBC	Vyepti ® Lundbeck Australia Pty Ltd
Continuing treatment				
Eptinezumab 100 mg IV infusion	1	1	Published Price $ [redacted] Effective Price: TBC	Vyepti ® Lundbeck Australia Pty Ltd

Category/Program:	GENERAL – General Schedule – Section 85
Prescriber type:	☐Dental ☒ Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Chronic migraine
Treatment phase:	Initial treatment ~~covering the first 12 weeks of treatment~~
Restriction Type	☒Authority Required – Streamlined
Clinical criteria:	Patient must have experienced an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months, prior to commencement of treatment with this drug for this condition AND Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with this drug for this condition
Treatment criteria	Must be treated by a neurologist AND Patient must not be undergoing concurrent treatment with the following PBS benefits: (i) botulinum toxin type A listed for this PBS indication, (ii) another drug in the same pharmacological class as this drug listed for this PBS indication.
Population criteria:	Patient must be aged 18 years or older.
Prescriber instructions:	Prophylactic migraine medications are propranolol, amitriptyline, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate or topiramate. AND Patient must have the number of migraine days per month documented in their medical records.
Administrative note:	*No increase in maximum quantity of number of units may be authorised* *No increase in the maximum number of repeats may be authorised* *Eptinezumab at a dose of 300 mg, once every twelve weeks, is not subsidised on the PBS.* *Special pricing arrangements apply*

Category/Program:	GENERAL – General Schedule – Section 85
Prescriber type:	☐Dental ☒ Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Chronic migraine
Treatment phase:	Continuing
Restriction Type	☒Authority Required – Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine days per month
Treatment criteria	Must be treated by a specialist neurologist or in consultation with a specialist neurologist AND Patient must not be undergoing concurrent treatment with the following PBS benefits: (i) botulinum toxin type A listed for this PBS indication, (ii) another drug in the same pharmacological class as this drug listed for this PBS indication.
Population criteria:	Patient must be aged 18 years or older.
Prescriber instructions:	Patient must have the number of migraine days per month documented in their medical records.
Administrative note:	*No increase in maximum quantity of number of units may be authorised* *No increase in the maximum number of repeats may be authorised* *Eptinezumab at a dose of 300 mg, once every twelve weeks, is not subsidised on the PBS.* *Special pricing arrangements apply*

Abbreviations: IV=intravenous, PBS= Pharmaceutical Benefits Scheme; SPA = special pricing arrangement proposed in p42 of the submission.
Source: Table 20, p 43; Table 21, p44, Table 22, p45 of the submission

3.2 The requested restriction was consistent with the evidence presented in the submission and the existing PBS listings for other calcitonin gene-related peptide (CGRP) inhibitors subsidised for treatment of CM, with the exception of a request to exclude the medication overuse headache (MOH) criterion currently applied to other CGRP inhibitors. The submission presented evidence that the efficacy and safety of eptinezumab relative to placebo was not affected by MOH status. The Advisory Committee on Medicines (ACM) of the TGA were also of the view that eptinezumab could potentially be a useful option in the MOH subgroup, who are generally refractory to all other migraine therapies (p33 TGA, Australian Public Assessment Report for Eptinezumab*).* In addition, the submission presented clinician input regarding the criterion for management of MOH stating that the existing requirement is open to interpretation and that detoxification prior to the commencement of a prophylactic therapy is associated with a number of disadvantages, such as potential delay in treatment commencement for patients who would otherwise benefit from initiation of a CGRP inhibitor. The pre-subcommittee response (PSCR) stated this change is requested in response to feedback from key opinion leaders suggesting that the current restriction could be interpreted to mean that patients with MOH should be weaned from multiple acute migraine therapies prior to the initiation of treatment with a CGRP inhibitor causing delays in treatment. The ESC considered it was unlikely patients were being weaned from other migraine treatments but noted removal of this from the CGRP inhibitors' restriction criteria was unlikely to have a significant impact on clinical practice.

3.3 Exclusion of the MOH criterion from the restriction for eptinezumab while retaining it in the restrictions for other CGRP inhibitors would imply a difference between the populations in which these treatments are effective (i.e., patients with MOH). The submission did not present evidence comparing effectiveness of eptinezumab with galcanezumab and fremanezumab in patients with MOH. The clinical trials for galcanezumab (CONQUER, REGAIN) and fremanezumab (FOCUS) enrolled patients with MOH and reported the proportion of patients with acute headache medication overuse at baseline (CONQUER, 65-68%; REGAIN, 63-64%; FOCUS, 52% (435/837)). The PSCR acknowledged it would be a matter for the PBAC to decide whether the evidence for the other CGRP inhibitor listings would also support exclusion of the MOH criterion.

3.4 The submission requested listing of eptinezumab 100 mg on the PBS. The product information (PI) recommends that patient benefit be assessed 3 to 6 months post treatment, with the need for dose escalation (to 300 mg) to be assessed within 3 months of treatment commencement. The ESC noted the proposed PBS maximum quantity would not permit the administration of 300 mg and agreed with the Secretariat's proposed addition of administrative advice stating no increase in the maximum quantity or number of units may be authorised. Additionally, the PSCR accepted the Secretariat's proposed administrative note: "Eptinezumab at a dose of 300 mg, once every twelve weeks, is not subsidised on the PBS".

3.5 The submission requested a special pricing arrangement, with the effective price to be determined based on cost-minimisation to the effective price of galcanezumab or fremanezumab (assuming they have the same effective price).

3.6 The submission requested a General Schedule listing and stated eptinezumab could be administered in a community setting. The PSCR stated the administration of eptinezumab by IV infusion could be performed in the community setting by GPs or by appropriately trained nurses. IV infusions are already performed in the community setting for other medicines, so the addition of eptinezumab will only require minor adjustments (such as an infusion set with an in-line or add-on sterile filter and an administration pump) with respect to the administration requirements. Eptinezumab is infused over approximately 30 minutes and the treating physician should observe or monitor patients during and after the infusion in accordance with normal clinical practice.

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

4 Population and disease

4.1 Migraine is a primary headache disorder, characterised by recurrent headache lasting 4 to 72 hours and often accompanied by symptoms such as nausea, vomiting and hypersensitivity to light and sound. CM is defined as 15 or more headache days per month for more than 3 months, and fulfilment of the International Classification of Headache Disorders 3rd Edition criteria for migraine on 8 or more days per month.

4.2 The submission noted that MOH is a condition affecting a subgroup of patients that will be eligible for treatment with eptinezumab. MOH can result from the frequent use of acute medicines or painkillers, such as triptans, ergotamines, opiates, non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol.

4.3 The target population is patients with treatment resistant CM, who have had an inadequate response, intolerance or contraindication to at least three prior preventative medications. The population presented by the submission was broadly consistent with the current PBS listings for botulinum toxin type A (herein referred to as botox), galcanezumab and fremanezumab with the exception of the request for the removal of the MOH criterion.

4.4 The submission's proposed clinical management algorithm placed eptinezumab as an alternative treatment to the PBS listed treatments for CM of botox, galcanezumab and fremanezumab.

4.5 The submission assumed CGRP inhibitors could be used sequentially. Previously, the PBAC considered that should another CGRP inhibitor be listed on the PBS the restriction for all CGRP inhibitors should be amended to exclude sequential use (except in the circumstance of intolerance) until such time that evidence is provided to the PBAC to demonstrate the clinical benefit and cost-effectiveness of sequential use (paragraph 5.13, galcanezumab PSD, November 2020). The PSCR noted that whilst

the PBAC have previously advised against sequential use of CGRP inhibitors, the PBS restrictions themselves do not exclude it.

4.6 Eptinezumab belongs to the same therapeutic class as galcanezumab and fremanezumab, which are both CGRP ligand antagonists. The evaluation considered this may imply a reduced likelihood of response to eptinezumab after patients fail prior treatment with galcanezumab and fremanezumab.

5 Comparator

5.1 The submission nominated galcanezumab and fremanezumab, CGRP inhibitors currently PBS listed for CM, as the main comparators.

5.2 If treatment with eptinezumab is substantially more costly than an alternative therapy or alternative therapies, the PBAC could only recommend listing of eptinezumab if it is satisfied that eptinezumab provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (National Health Act 1953, Section 101(3B)).

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 (85), health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described the benefit of having additional options available to treat chronic migraine and the need for better treatment options due to the debilitating nature of the condition. A number of comments related to potential advantages or disadvantages of a treatment requiring IV infusion, and/or access to a clinic for administration every 3 months.

6.3 The PBAC noted the advice received from Migraine and Headache Australia, ANZ Headache Society and Migraine Australia which all emphasised the importance of having a variety of treatment options available for patients with chronic migraine. ANZ Headache Society stated the mode of administration and rapid onset of eptinezumab may be of benefit to some patients. Migraine and Headache Australia stated that eptinezumab has efficacy in medication overuse headache. Migraine Australia strongly advocated for better medical services for people with migraine, and in particular, for the PBS listing of eptinezumab.

Clinical trials

6.4 The submission was based on an ITC of eptinezumab with galcanezumab and fremanezumab, using placebo as the common comparator. The submission presented

seven randomised controlled trials (RCTs) as the basis of the ITC, as detailed in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
DELIVER (NCT04418765)	Interventional, randomised, double-blind, parallel group, placebo-controlled study with an extension period to evaluate the efficacy and safety of eptinezumab for the prevention of migraine in patients with unsuccessful prior preventive treatments	Clinical Study Report, 10 December 2021
PROMISE-2 (NCT02974153)	A Parallel Group, Double-Blind, Randomised, Placebo-Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of ALD403 Administered Intravenously in Patients with Chronic Migraine.	Clinical Study Report 19 September 2018
	Lipton RB, Goadsby PJ, Smith J, Schaeffler BA, Biondi DM, Hirman J, Pederson S, Allan B, Cady R. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2.	Neurology 2020, 94(13): E1365-E1377
Study 005 (NCT02275117)	A Parallel Group, Double-Blind, Randomised, Placebo-Controlled, Dose-Ranging Phase 2 Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of ALD403 Administered Intravenously in Patients with Chronic Migraine.	Clinical Study Report 11 July 2017
	Dodick DW, Lipton RB, Silberstein S, Goadsby PJ, Biondi D, Hirman J, Cady R, Smith J. "Eptinezumab for prevention of chronic migraine: A randomized phase 2b clinical trial."	Cephalalgia 2019, 39(9): 1075-1085
Galcanezumab trials		
CONQUER (NCT03559257)	Mulleners, W. M., Kim, B. K., Láinez, M. J. A., Lanteri-Minet, M., Pozo-Rosich, P., Wang, S., Detke, H. C. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial.	The Lancet Neurology 2020, 19(10), 814-825.
	Reuter, U., et al. "Galcanezumab in Patients with Multiple Previous Migraine Preventive Medication Category Failures: Results from the Open-Label Period of the CONQUER Trial."	Advances in Therapy 2021, 38(11): 5465-5483.
	Okonkwo, R., A. Tockhorn-Heidenreich, C. Stroud, M.-A. Paget, M. S. Matharu and C. Tassorelli. "Efficacy of galcanezumab in patients with migraine and history of failure to 3–4 preventive medication categories: subgroup analysis from CONQUER study."	The Journal of Headache and Pain 2021, 22(1): 113.
	Maizels, M, Buse D, Jedynak JP, Hand A et al. Assessment of anxiety and depression in a randomized, double-blind, placebo-controlled study of galcanezumab in adults with treatment-resistant migraine: Results from the CONQUER study.	Journal of the Neurological Sciences 2019; 405 (Supplement):129-130.
REGAIN (NCT02614261)	Detke, H. C., Wang, S., Skljarevski, V., Ahl, J., Millen, B., Aurora, S. K., & Yang, J. A phase 3 placebo-controlled study of galcanezumab in patients with chronic migraine: Results from the 3-month double-blind treatment phase of the REGAIN study.	Headache 2017, 57(8): 1336-1337
	Ruff DD, Ford JH, Tockhorn-Heidenreich A, Sexson M et al. Efficacy of galcanezumab in patients with chronic migraine and a history of preventive treatment failure.	Cephalalgia 2019; 39(8):931-944.
Fremanezumab trials		
FOCUS (NCT03308968)	Ferrari, M. D., et al. "Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial."	The Lancet 2019, 394(10203): 1030-1040

Trial ID	Protocol title/ Publication title	Publication citation
	Spierings, E. L. H., M. Kärppä, X. Ning, J. M. Cohen, V. R. Campos, R. Yang and U. Reuter. "Efficacy and safety of fremanezumab in patients with migraine and inadequate response to prior preventive treatment: subgroup analyses by country of a randomized, placebo-controlled trial."	J Headache Pain 2021, 22(1): 26.
	Pazdera, L., J. M. Cohen, X. Ning, V. R. Campos, R. Yang and P. Pozo-Rosich (2021). "Fremanezumab for the Preventive Treatment of Migraine: Subgroup Analysis by Number of Prior Preventive Treatments with Inadequate Response."	Cephalalgia 2021, 41(10): 1075-1088.
	Ashina, M., J. M. Cohen, M. Galic, V. R. Campos, S. Barash, X. Ning, Y. Kessler, L. Janka and H. C. Diener (2021). "Efficacy and safety of fremanezumab in patients with episodic and chronic migraine with documented inadequate response to 2 to 4 classes of migraine preventive medications over 6 months of treatment in the phase 3b FOCUS study."	J Headache Pain 2021, 22(1): 68.
	MaassenVanDenBrink, A., G. M. Terwindt, J. M. Cohen, S. Barash, V. R. Campos, M. Galic, X. Ning and M. Kärppä (2021). "Impact of age and sex on the efficacy of fremanezumab in patients with difficult-to-treat migraine: results of the randomized, placebo-controlled, phase 3b FOCUS study."	J Headache Pain 2021, 22(1): 152.
HALO (NCT02621931)	Silberstein, S. D., D. W. Dodick, M. E. Bigal, P. P. Yeung, P. J. Goadsby, T. Blankenbiller, M. Grozinski-Wolff, R. Yang, Y. Ma and E. Aycardi (2017). "Fremanezumab for the Preventive Treatment of Chronic Migraine.	New England Journal of Medicine 2017, 377(22): 2113-2122.
	Silberstein, S. D., J. M. Cohen, M. J. Seminerio, R. Yang, S. Ashina and Z. Katsarava. "The impact of fremanezumab on medication overuse in patients with chronic migraine: subgroup analysis of the HALO CM study	J Headache Pain 2020, 21(1): 114.
	Winner, P. K., E. L. H. Spierings, P. P. Yeung, E. Aycardi, T. Blankenbiller, M. Grozinski-Wolff, R. Yang and Y. Ma (2019). "Early Onset of Efficacy With Fremanezumab for the Preventive Treatment of Chronic Migraine."	Headache 2019, 59(10): 1743-1752.
	Silberstein, S. D., J. M. Cohen, R. Yang, S. K. Gandhi, E. Du, A. E. Jann and M. J. Marmura (2021). "Treatment benefit among migraine patients taking fremanezumab: results from a post hoc responder analysis of two placebo-controlled trials."	J Headache Pain 2021, 22(1): 2.

Source: Table 25 of the submission; Attachment 3 of the submission.

6.5 The results of the seven trials and subsequent ITC were presented by the number of failed prior preventative migraine medications (≥ 0; 2 to 4; ≥ 3). Three of the trials presented included patients with ≥ 3 prior preventative migraine medications as a subgroup (DELIVER for eptinezumab; CONQUER and REGAIN for galcanezumab). The listing requested for eptinezumab relies on the presentation of subgroup analyses from DELIVER, CONQUER and REGAIN for patients using ≥ 3 prior preventative migraine medications, which is the population that aligns with the proposed PBS listing and that of the comparators. The sources of the main evidence for each drug and by subgroup are summarised in Table 3.

Table 3: Summary of source of the main clinical evidence used in the submission

Intervention Comparison	Trial ID	Subgroups: prior preventative treatment		
		≥ 0	2 to 4	≥ 3
Eptinezumab	DELIVER [a]	-	Yes (subgroup)	Yes (subgroup)
Eptinezumab 100 mg q12w vs eptinezumab 300 mg q12w vs placebo q12w	Study 005	Yes (ITT)	-	-
	PROMISE-2	Yes (ITT)	-	-
Galcanezumab	CONQUER [b]	-	Yes (subgroup)	Yes (subgroup)
Galcanezumab 120 mg monthly vs placebo monthly	REGAIN	Yes (ITT)	-	Yes (subgroup)
Fremanezumab	FOCUS	-	Yes (subgroup)	-
Fremanezumab 225 mg monthly vs placebo	HALO	Yes (ITT)	-	-

Abbreviations: ITT = intention to treat; q12w = every 12 weeks

Source: Compiled during the evaluation; Figure 6 p64 of the submission.

Note: The clinical trials shown may have included treatment groups other than those included in this table. Those shown were the main source of evidence for each of the drugs shown in the respective treatment settings.

a DELIVER whole population (FAS) analysis included patients with EM and CM. The subgroups presented only included patients with CM.

b CONQUER ITT analysis included patients with EM and CM. The subgroups presented only included patients with CM.

6.6 The pivotal trial for galcanezumab in CM reviewed by the PBAC was REGAIN (paragraph 6.7, galcanezumab PSD, July 2019). CONQUER was reviewed by PBAC for the galcanezumab submission for episodic migraine (paragraph 6.4, galcanezumab PSD, November 2020). The pivotal study for fremanezumab reviewed by the PBAC was FOCUS, which enrolled patients with EM and CM (paragraph 6.4, fremanezumab PSD November 2019). The PBAC has not reviewed HALO (Silberstein 2017), as this study was not presented in the submission for fremanezumab (paragraph 6.4, fremanezumab PSD, November 2019).

6.7 The key features of the direct randomised trials are summarised in Table 4.

Table 4: Key features of the included evidence – indirect comparison

Trial	N	Patient population[a]	Risk of bias	Design/ duration	Outcomes
Eptinezumab vs. placebo					
DELIVER	892	Chronic migraine and episodic migraine, failed 2 to 4 preventative migraine medications	Low	R, DB, MC, PC (24 weeks); with OLE 48 weeks[b]; Treatment arms (EPTI 100 mg; EPTI 300 mg; PBO).	Change from baseline in MMDs; Responder: ≥ 50% reduction in MMDs
	405	Subgroup: chronic migraine, failed 2 to 4 preventative migraine treatments	High		
	166	Subgroup: chronic migraine, failed ≥ 3 preventative migraine treatments	High		
PROMISE-2	1,121	Chronic migraine	Low	R, DB, MC, PC (12 weeks); with 20 week follow-up; Treatment arms (EPTI 100 mg; EPTI 300 mg; PBO).	Change from baseline in MMDs; Responder: ≥ 50% reduction in MMDs
Study 005	398	Chronic migraine	Unclear	R, DB, MC, PC, single dose (12 weeks); with 54 week follow-up; Treatment arms (EPTI 100 mg; EPTI 300 mg; PBO).	Responder: ≥ 75% reduction in MMDs; Change from baseline in MMDs.
Meta-analysis	956	Included PROMISE-2 and Study 005 (Treatment arms: eptinezumab 100 mg and placebo).			Change from baseline in MMDs; Responder: ≥ 50% reduction in MMDs
Galcanezumab vs. placebo					
CONQUER	462	Chronic migraine and episodic migraine, failed 2 to 4 preventative treatments	Low	R, DB, MC, PC (3 months); with OLE 3 months, Treatment arms (GAL 120 mg; PBO).	Change from baseline in MMDs; Responder: ≥ 50% reduction in MMDs
	193	Subgroup: chronic migraine, failed 2 to 4 preventative migraine treatments	High		
	86	Subgroup: chronic migraine, failed ≥ 3 preventative migraine treatments	High		
REGAIN	1,113[c]	Chronic migraine, failure to respond to ≤ 3 preventative migraine treatments classes	Low	R, DB, MC, PC (3 months); with OLE 9 months, Treatment arms (GAL 120 mg; GAL 240 mg; PBO).	Change from baseline in MMDs; Responder: ≥ 50% reduction in MMDs
	139	Subgroup: failure to respond to three preventative migraine treatments classes	High		
Meta-analysis	223	Included CONQUER and REGAIN (subgroups: chronic migraine ≥ 3 preventative migraine treatments; treatment arms: galcanezumab 120 mg and placebo)			Change from baseline in MMDs; Responder: ≥ 50% reduction in MMDs
Fremanezumab vs. placebo					
FOCUS	838[d]	Chronic migraine and episodic migraine, failed 2 to 4 preventative migraine medications	Low	R, DB, MC, PC (12 weeks); with OLE 12 weeks, Treatment arms (FREM monthly; FREM 3-monthly; PBO)	Change from baseline in MMDs
	340	Subgroup: chronic migraine, failed 2 to 4 preventative migraine medications	High		
HALO	1,130[e]	Chronic migraine, excluded if patient failed ≥2 of 4 of	Low	R, DB, MC, PC (12 weeks), Treatment arms (FREM monthly;	Change from baseline in MHDs

Trial	N	Patient population[a]	Risk of bias	Design/ duration	Outcomes
		the clusters of preventive medications		FREM 3-monthly; PBO)	(of at least moderate severity) and MMDs

Abbreviations: DB = double blind; MC = multi-centre; MHD = monthly headache days; MMD = monthly migraine days; OL = open label; OLE = open label extension; PC = placebo-controlled; R = randomised.
Source: Table 28 p74, Table 27 pp67-70, pp71-73 of the submission
Notes: a Chronic migraine: baseline MHDs ≥ 15 and MMDs≥ 8; episodic migraine: baseline MHDs ≤ 14 and MMDs≥ 4.
b Results reported up to 24 weeks for DELIVER; OLE is ongoing.
c Three arms in the trial, however, two arms (n=838), GAL 120 mg and PBO, were presented in the submission.
d Three arms in the trials, however, two arms (n=562), FREM monthly and PBO, were presented in the submission; N for subgroup is for the two arms presented.
e Three arms in the trial, however, two arms (n=754), FREM monthly and PBO, were presented in the submission; N for subgroup is for the two arms presented.

6.8 Except for Study 005, the overall risk of bias for all trials was low. Protocol deviations were high in Study 005; patients from one study site were excluded from the primary efficacy analysis due to concerns regarding the data. PROMISE-2 and Study 005 do not directly inform the PBS listing of interest which is for the treatment of patients with ≥ 3 prior preventative treatments.

6.9 There are transitivity issues with the trials included for the population of patients with ≥ 0 prior preventative treatments (PROMISE-2, Study 005, REGAIN, and HALO).

- Exposure to prior preventative treatments: The populations from Study 005 and PROMISE-2 were not specific to the population for which PBS listing is being sought i.e., no requirement for patients to have failed any preventative migraine treatments prior to baseline as it was not part of the eligibility criteria. A considerably higher proportion of patients in REGAIN and HALO had received prior preventative migraine treatments compared with the trials for eptinezumab, PROMISE-2 and Study 005.
- Concurrent preventative treatments: In comparing the placebo arms of the trials, PROMISE-2 included a higher proportion of patients on concomitant treatment (45%) compared to REGAIN (15%), and HALO (21%). Concurrent preventative treatments were permitted in Study 005, but the proportion of patients using concomitant treatment was not reported.
- Outcomes reported in the placebo groups: In REGAIN and HALO, the change from baseline in MMDs, MHDs, and proportion of patients with ≥ 50% reduction in MMDs were lower than those reported in PROMISE-2 and Study 005.

The differences in the clinical characteristics pertaining to prior and concomitant preventative treatments, and outcomes reported for the placebo groups may influence the transitivity of the trials. The differences between REGAIN and HALO with the eptinezumab trials, PROMISE-2 and Study 005, means that it may not be suitable to include evidence from those trials in the ITC.

6.10 The overall risk of bias presented for the subgroups of DELIVER, CONQUER, REGAIN and FOCUS was high. The risk of bias was considered to be high for the subgroup analyses presented in some of these trials as assessed at prior PBAC meetings

(paragraph 6.8, Table 3, galcanezumab PSD, July 2019). Due to the relatively small sample size of the patient population included, there is an increased risk of type II errors (such as would occur if the trials failed to detect an effect for treatment even where one actually existed). Results should be interpreted with caution due to the small sample size of the subgroups used from the trials and post-hoc nature of the analyses. Although these subgroup analyses are a high risk of bias, the results for the subgroup of patients with CM who have failed three or more preventative migraine treatments are the most informative for decision making.

6.11 The submission relied on data from the subgroup of patients with MOH to justify its proposal that such patients be eligible to access PBS listed eptinezumab. However, that evidence was based on approximately 110 (12%) patients in DELIVER, which is the trial including the population consistent with the listing being requested for eptinezumab.

Comparative effectiveness

6.12 A summary of the effectiveness for eptinezumab, galcanezumab, and fremanezumab in patients with CM is presented in Table 5.

Table 5: Change from baseline in MMDs (12 weeks/3 months)

	Trial ID	EPTI/GAL/FREM			Placebo			LSM difference (95% CI)
		N	Baseline mean (SD)	LSM change (SD)	N	Baseline mean (SD)	LSM change (SD)	
Whole trial population								
EPTI vs PBO	DELIVER[d]	*299*	13.8 (5.6)	-4.8 (NR)[a]	298	13.9 (5.7)	-2.1 (NR)[a]	-2.7 (-3.4, -2.0)
	PROMISE-2	356	16.1 (4.6)	-7.8 (6.1)	366	16.2 (4.6)	-5.8 (6.4)	-2.0 (-2.9, -1.1)
	Study 005	118	16.9 (4.8)	-7.7 (6.9)	116	16.4 (5.1)	-5.6 (6.6)	-2.1 (-3.8, -0.4)
GAL vs PBO	CONQUER[d]	*232*	13.4 (6.1)	-4.1 (NR)[a]	230	13.0 (5.7)	-1.0 (NR)[a]	−3.1 (-3.9, -2.3)
	REGAIN	273	19.4 (4.3)	-4.8 (6.6)	538	19.6 (4.6)	-2.7 (9.3)	-2.1 (-2.9, -1.3)
FREM vs PBO	HALO	375	16.0 (5.2)	-5.0 (7.7)	371	16.4 (5.2)	-3.2 (7.7)	-1.8 (-2.6, -1.0)[b]
Subgroup of patients with chronic migraine ≥3 prior treatment failures								
EPTI vs PBO	DELIVER	56	20.0 (3.5)	-6.1 (7.3)	56	19.7 (3.9)	-1.7 (7.4)	-4.4 (-7.15, -1.65)[b]
GAL vs PBO	CONQUER	42	21.4 (4.7)	-6.7 (7.6)	42	20.6 (4.4)	-1.6 (7.3)	-5.1 (-8.3, -1.9)[b]
	REGAIN	103	NR	-5.6 (5.8)	36	NR	-0.4 (7.7)	-5.2 (-7.7, -2.8)[b]
Subgroup of patients with chronic migraine 2 to 4 prior treatment failures								
EPTI vs PBO	DELIVER[d]	137	18.5 (3.9)	-6.5 (8.2)	134	18.7 (4.0)	-3.3 (8.1)	-3.3 (-4.5, -2.0)
GAL vs PBO	CONQUER	95	19.2 (4.7)	-6.0 (6.8)	98	18.1 (4.7)	-2.2 (5.9)	-3.7 (-5.2, -2.2)
FREM vs PBO	FOCUS	173	NR	-4.5 (3.0)[c]	167	NR	-0.7 (3.3)[c]	-3.8 (-4.8, -2.8)
Subgroup: patients with chronic migraine ≥3 prior treatment failures and MOH								
EPTI vs PBO	DELIVER[d]	38	17.0 (NR)	-5.6 (5.84)	37	18.9 (NR)	-2.3 (6.03)	-3.3 (-5.9, -0.7)
	PROMISE-2	139	16.7 (4.6)	-8.4 (6.3)	145	16.7 (4.4)	-5.4 (6.7)	-3.0 (-4.6, -1.5)
	Study 005	59	17.6 (4.8)	-8.2 (6.4)	62	16.7 (5.0)	-5.2 (6.9)	-3.0 (-5.4, -0.6)

Source: Compiled during the evaluation using: Table 33 p92, Table 56 p147 of the submission; MOH: Table 74 p175, Table 75 p176, Table 76 p177 of the submission; DELIVER CSR, Table 31 p188, Panel 20 p83; DELIVER Subgroup report Table 2 p3, Table 4 p4, Table 6 p6, Table 8 p7; PROMISE-2 CSR Table 14.2.2.3.4 p418; Study 005 CSR Table 14.2.2.3.4 p1411; CONQUER Mulleners 2020 Table p p819 and Table 2 p821; FOCUS, paragraph 6.17, Table 4, Fremanezumab PSD.

Abbreviations: CI = confidence interval; EPTI = eptinezumab; FREM = fremanezumab; GAL = galcanezumab; LSM = least squares mean; MMD = monthly migraine days; MOH = medication overuse headache; n = number of participants reporting data; N = total participants in group; NR = not reported; PBO = placebo; SD = standard deviation.

Notes: a Standard errors for the LSM change were reported in DELIVER and CONQUER.

b Two results were presented: MMRM LSM difference reported in the key publications and RevMan results as calculated by the submission. Results calculated in RevMan is presented in the table.

c Calculation of standard deviation by the submission was not verified during the evaluation.

d Results for the whole trial population for DELIVER and CONQUER included patients with episodic migraine and were extracted during evaluation. For DELIVER, the N and results present are from the DELIVER subgroup report where change in MMD from baseline compared with placebo is from the MMRM by 12-week intervals. The DELIVER subgroup report does give the results by the 4-week intervals, which are different from the results of the 12-week intervals.

6.13 The submission did not nominate a specific non-inferiority margin but noted that a minimal clinically important difference (MCID) of around 2 to 3 days for MHD had previously been accepted by the PBAC, based on the upper 95% confidence interval for mean differences for change in headache days assessed in the PBAC's consideration of botox to treat chronic migraine (Section 12, p.5, botox PSD, July 2012).

6.14 Based on the results from DELIVER, eptinezumab is superior to placebo in patients with CM who have failed ≥ 3 preventative migraine treatment with respect to the change from baseline in MMDs. The results for the comparator trials, as previously reviewed by the PBAC, indicate that both galcanezumab and fremanezumab are superior to placebo in patients with CM who have failed ≥ 3 preventative migraine treatment with respect to the change from baseline in MMDs.

6.15 Results for treatment over 24 weeks with eptinezumab 100 mg compared with placebo from DELIVER were presented for the subgroups of patients with prior treatment failures (2-4; ≥ 3). The change from baseline in MMDs (2-4 treatment failures, MMRM LSM difference: -3.6 (95% CI, -5.0 to -2.2); ≥ 3 treatment failures, MMRM LSM difference: -4.5 (95% CI, -6.8 to -2.3)) at 12 weeks was sustained up to 24 weeks. More patients treated with eptinezumab 100 mg had a 50% or more reduction in MMDs compared with placebo after 24 weeks (2-4 treatment failures: OR 2.76, 95% CI 1.62 to 4.70; ≥ 3 treatment failures: OR 3.07, 95% CI 1.28 to 7.33). Evidence from the DELIVER subgroups of patients with 2 to 4 and ≥ 3 prior treatment failures supported the claim of superior effectiveness compared with placebo over a treatment period of 24 weeks.

6.16 Treatment with eptinezumab 100 mg was associated with statistically significant improvements in the HIT-6 compared to placebo in patients with CM with 2 to 4 prior treatment failures (MMRM LSM difference: -3.6 (95% CI, -5.2 to -1.9) and in patients with ≥ 3 treatment failures (MMRM LSM difference: -3.5 (95% CI, -6.1 to -1.0).

6.17 The submission stated that the difference observed between the MOH subgroups and the PROMISE-2 (full analysis population (FAP)), Study 005 (modified FAP), and CM population in DELIVER were not statistically significant.

<u>Indirect comparison: patients with CM with ≥ 0 preventative treatment failures</u>

6.18 The submission stated the results of the indirect comparison supported the claim that eptinezumab is non-inferior to galcanezumab and fremanezumab on the basis that there were no statistically significant differences for change in MMDs, change in MHDs and response rate (patients with ≥ 50% reduction in MMDs).

6.19 There were transitivity issues between the eptinezumab trials (PROMISE-2 and Study 005), the galcanezumab trial (REGAIN) and the fremanezumab trial (HALO) (as discussed in paragraph 6.9). Data from this comparison, which is informed by patients with ≥ 0 prior preventative treatments does not directly inform the PBS listing of interest which is for the treatment of patients with ≥ 3 prior preventative treatments.

<u>Indirect comparison: patients with CM with 2 to 4 preventative treatment failures</u>

6.20 The results of the ITC for patients with CM after 2 to 4 preventative treatment failures are presented in Table 6. The submission noted that the differences between eptinezumab and galcanezumab, for the change from baseline in MMDs and the response rate (patients with ≥ 50% reduction in MMDs) were not statistically significant. The submission claimed that eptinezumab 100 mg is non-inferior to galcanezumab 120 mg, and fremanezumab 225 mg on the basis of the outcomes

presented in the ITC. However, the upper confidence intervals (UCI) for the change in MMD (EPTI vs GAL: UCI, 3.25 days; EPTI vs FREM: UCI, 2.67), exceeded the MCID of 2 days. Thus, the evaluation considered it is not possible to rule out a clinically meaningful difference between therapies with respect to MMD.

Table 6: Indirect comparison–patients with chronic migraine with 2 to 4 preventative treatment failures

Relative impact on MMD (12 weeks/3 months)					
Comparison	**Trial ID**	**Change from baseline in MMDs, mean (SD)**			**Treatment effect LSM (95% CI)**
		EPTI 100 mg	**Placebo**	**GAL 120 mg / FREM 225 mg**	
EPTI vs PBO	DELIVER (subgroup)	-6.5 (8.2); n=137	-3.3 (8.1); n=134	-	-3.20 (-5.14, -1.26)
GAL vs PBO	CONQUER (subgroup)	-	-2.2 (5.9); n=98	-6.0 (6.8); n=95	-3.80 (-5.61, -1.99)
FREM vs PBO	FOCUS (subgroup)	-	-0.7 (3.3); n=167	-4.5 (3.0); n=173	-3.82 (-4.49, -3.15)
Indirect estimate of effect adjusted for the common reference, mean (95% CI)					
EPTI vs GAL: DELIVER (subgroup), CONQUER (subgroup)					0.6 (-2.05, 3.25) (p = 0.658)
EPTI vs FREM: DELIVER (subgroup), FOCUS (subgroup)[c]					0.62 (-1.43, 2.67) (p=0.554)

Response rate: patients with ≥ 50% reduction in MMDs (12 weeks/3months)				
Comparison	**Trial ID**	**EPTI /GAL n/N (%)**	**Placebo n/N (%)**	**Treatment effect OR[d] (95% CI)**
EPTI vs PBO	DELIVER (subgroup)	52/137 (38.0)	21/134 (15.7)	3.29 (1.84, 5.88)
GAL vs PBO	CONQUER (subgroup)[d]	30/95 (31.6)[a]	9/98 (9.2)[a]	4.56 (2.03, 10.27)[b]
Indirect estimate of effect adjusted for the common reference (EPTI vs GAL): DELIVER (subgroup) and CONQUER (subgroup)				0.72 (0.27, 1.96) (p = 0.521) [d]

Source: Table 49 p137, Table 82 p187, Table 83 p188 of the submission.
Abbreviations: CI = Confidence interval; n = number of participants with event; N = total number of participants in group; OR = Odds ratio; PBO = placebo; MMD = monthly migraine days; WMD = weighed mean difference.
a CONQUER: Submission reported that the number of patients were calculated in RevMan. For this outcome, Mulleners 2020 reported the mean percentage of patients: placebo: 8.9% (2.4); galcanezumab 120 mg 32.0% (4.0) (Table 2 p821).
b CONQUER: Submission reported the odds ratio results calculated by the submission in RevMan. The odds ratio presented in Mulleners 2020 for the patients with ≥ 50% reduction in MMDs was 4.8 [95% CI: 2.4, 9.6].
c Indirect comparison with FOCUS for this outcome were extracted using Vyepti Data Extraction worksheet provided with the submission
d numbers corrected in PSCR

Indirect comparison: patients with CM with ≥ 3 preventative treatment failures

6.21 The results of the ITC for patients with ≥ 3 preventative treatment failures are presented in Table 7. The submission noted that the differences for the change from baseline in MMDs and the response rate (patients with ≥ 50% reduction in MMDs) were not statistically significant. The submission claimed that eptinezumab 100 mg is non-inferior to galcanezumab 120 mg on the basis of the outcomes presented in the indirect comparison. The upper confidence interval for the change in MMD (EPTI versus GAL: UCI, 4.16 days) exceeded the MCID of 2 days. Thus, the evaluation considered it is not possible to rule out a clinically meaningful difference between the therapies with respect to treatment efficacy.

Table 7: Indirect comparison–patients with chronic migraine with ≥ 3 preventative treatment failures

Relative impact on MMD (12 weeks/3 months)					
Comparison	**Trial ID**	**Change from baseline in MMDs, mean (SD)**			**Treatment effect LSM (95% CI)**
		EPTI 100 mg	**Placebo**	**GAL 120 mg**	
EPTI vs PBO	DELIVER (subgroup)	-6.1 (7.3); n=55	-1.7 (7.4); n=55	-	-4.40 (-7.15, -1.65)
GAL vs PBO	CONQUER (subgroup)	-	-1.6 (7.3); n=42	-6.7 (7.6); n=42	-5.10 (-8.27, -1.93)
	REGAIN (subgroup)	-	-0.4 (7.7); n=103	-5.6 (5.8); n=36	-5.25 (-7.67, -2.83)
Meta-analysis	CONQUER (subgroup), REGAIN (subgroup) I^2= 0%; p=0.94				-5.20 (-7.12, -3.27)
Indirect estimate of effect adjusted for the common reference, mean (95% CI)					
EPTI vs GAL: DELIVER (subgroup), CONQUER (subgroup), REGAIN (subgroup)					0.8 (-2.56, 4.16) (p = 0.640)

Response rate: patients with ≥ 50% reduction in MMDs (12 weeks/3months)				
Comparison	**Trial ID**	**EPTI /GAL n/N (%)**	**Placebo n/N (%)**	**Treatment effect OR[d] (95% CI)**
EPTI vs PBO	DELIVER (subgroup)	17/56 (30.4)	5/56 (8.9)	4.45 (1.51, 13.10)
GAL vs PBO	CONQUER (subgroup)	17/42 (40.5)	4/42 (9.5)	6.46 (1.94, 21.46)
	REGAIN (subgroup)	10/36 (27.8)	6/103 (5.8)	6.22 (2.07, 18.69)
Meta-analysis	CONQUER (subgroup), REGAIN (subgroup) I^2= 0%; p=0.96			6.33 (2.81, 14.24)
Indirect estimate of effect adjusted for the common reference (EPTI vs GAL): DELIVER (subgroup), CONQUER (subgroup), REGAIN (subgroup)				0.703 (0.182, 2.715) (p = 0.609)

Source: Figure 33 p180, Table 85 p191, Figure 34 p180, Table 86 p192 of the submission.
Abbreviations: CI = Confidence interval; n = number of participants with event; N = total number of participants in group; OR = Odds ratio; PBO = placebo; MMD = monthly migraine days; WMD = weighed mean difference.

Comparative harms

6.22 A summary of the adverse events (AEs) for eptinezumab, galcanezumab and fremanezumab is presented in Table 8.

6.23 Safety results reported for DELIVER included patients with CM and EM over a 24-week period. The overall incidence of treatment emergent adverse events (TEAEs) was similar across treatment groups (~40%). The most common TEAEs were COVID-19 (approximately 6% in each treatment group), nasopharyngitis (placebo: 1.0%; eptinezumab 100 mg: 1.7%), and fatigue (placebo: 1.3%; eptinezumab 100 mg: 0.7%). The majority of TEAEs reported were mild or moderate in severity; only a small proportion were classified as severe (placebo: 0.3%; eptinezumab 100 mg: 1.7%) (DELIVER CSR Table 111 p298).

6.24 The most frequently reported TEAEs in PROMISE-2 were nasopharyngitis (placebo: 6%; eptinezumab 100 mg: 5%), upper respiratory tract infection (URTI) (placebo: 5%; eptinezumab 100 mg: 4%), sinusitis (placebo: 4%; eptinezumab 100 mg: 2%), and migraine (placebo: 4%; eptinezumab 100 mg: 2%). In Study 005, the most common TEAEs were URTI (placebo: 5.0%; eptinezumab 100 mg: 6.6%) and dizziness (placebo: 7.4% eptinezumab 100 mg: 9.8%).

6.25 The submission claimed that eptinezumab, galcanezumab, and fremanezumab have similar safety profiles with similar incidences of TEAEs between treatment and

placebo groups. The incidences of SAEs and AEs leading to study drug discontinuations were low in all trials. No deaths were reported in any of the trials. Safety results across the trials are reported for the Safety/Full Analysis Population/Intention to treat populations.

Table 8: Summary of AEs in the trials

Trial	Any TEAE				Any serious TEAE				AEs resulting in discontinuation			
	Active n/N (%)	Placebo n/N (%)	RR (95% CI)	RD (95% CI)	Active n/N (%)	Placebo n/N (%)	RR (95% CI)	RD (95% CI)	Active n/N (%)	Placebo n/N (%)	RR (95% CI)	RD (95% CI)
Eptinezumab												
DELIVER 100 mg	127/299 (42.5)	119/298 (39.9)	1.06 (0.88, 1.29)	0.03 (-0.05, 0.10)	5/299 (1.7)	4/298 (1.3)	1.25 (0.34, 4.59)	0.00 (-0.02, 0.02)	1/299 (0.3)	1/298 (0.3)	1.00 (0.06, 15.86)	0.00 (-0.01, 0.01)
Study 005 100 mg	70/122 (57.4)	68/121 (56.2)	1.02 (0.82, 1.27)	0.01 (-0.11, 0.14)	4/122 (3.3)	1/121 (0.8)	3.97 (0.45, 34.99)	0.02 (-0.01, 0.06)	2/122 (1.6)	0/121 (0)	4.96 (0.24, 102.24)	0.02 (-0.01, 0.04)
PROMISE-2 100 mg	155/356 (43.5)	171/366 (46.7)	0.93 (0.79, 1.09)	-0.03 (-0.10, 0.04)	3/356 (0.8)	3/366 (0.8)	1.03 (0.21, 5.06)	0.00 (-0.01, 0.01)	3/356 (0.8)	2/366 (0.6)	1.54 (0.26, 9.17)	0.00 (-0.01, 0.02)
Galcanezumab												
CONQUER	119/232 (51.3)	122/230 (53.0)	0.97 (0.81, 1.15)	-0.02 (-0.11, 0.07)	2/232 (0.9)	2/230 (0.9)	0.99 (0.14, 6.98)	0.00 (-0.02, 0.02)	1/232 (0.4)	0/230 (0)	2.97 (0.12, 72.63)	0.00 (0.00, 0.01)
REGAIN	159/273 (58.2)	279/558 (50.0)	1.16 (1.02, 1.33)	0.08 (0.01, 0.15)	1/273 (0.4)	4/558 (0.7)	0.51 (0.06, 4.55)	0.00 (-0.01, 0.01)	NR	NR	NR	NR
Fremanezumab												
FOCUS	129/285 (45.3)	134/277 (48.4)	0.94 (0.78, 1.12)	-0.03 (-0.11, 0.05)	4/285 (1.4)	4/277 (1.4)	0.97 (0.25, 3.85)	0.00 (-0.02, 0.02)	4/285 (1.4)	3/277 (1.1)	1.30 (0.29, 5.74)	0.00 (-0.02, 0.02)
HALO	270/379 (71.2)	240/375 (64.0)	1.11 (1.01, 1.23)	0.07 (0.01, 0.14)	5/379 (1.3)	6/375 (1.6)	0.82 (0.25, 2.68)	0.00 (-0.02, 0.01)	7/379 (1.9)	8/375 (2.1)	0.87 (0.32, 2.36)	0.00 (-0.02, 0.02)

Abbreviations: AE = adverse event; CI = confidence interval; NR = not reported; RD = risk difference; RR = risk ratio; TEAE = treatment emergent adverse event.
Source: Table 65 p156 of the submission.

Benefits/harms

6.26 A summary of the benefits and harms is not presented given the non-inferiority nature of the claim for eptinezumab compared with galcanezumab and fremanezumab.

Clinical claim

6.27 The submission described eptinezumab 100 mg q12w as non-inferior in terms of effectiveness and safety compared with galcanezumab 120 mg monthly and fremanezumab 225 mg monthly.

6.28 The evaluation considered the claim for efficacy was not adequately supported by the evidence presented in the submission for the following reasons:

- The difference in the primary outcome, MMDs, between eptinezumab 100 mg and galcanezumab 120 mg did not meet the MCID of 2-3 days for:
  - Patients with 2 to 4 prior preventative treatment failures: The upper confidence interval for the change in MMD (EPTI vs GAL: UCI, 3.25 days; EPTI vs FREM: UCI, 2.67).
  - Patients with ≥ 3 prior preventative treatment failures: The upper confidence interval for the change in MMD (EPTI vs GAL: 4.16 days).

  On this basis, the evaluation considered the possibility of a clinically meaningful difference in outcomes between eptinezumab and galcanezumab, and eptinezumab and fremanezumab cannot be excluded. The efficacy was collected over a short period of time (12 weeks); with outcomes from the eptinezumab trials reported up to a maximum of 24 weeks. Short-term results for an ongoing chronic condition, particularly from a small sample size based on the subgroups presented, may not be generalisable to longer-term efficacy.

6.29 The submission described eptinezumab 100 mg q12w as non-inferior in terms of safety compared with galcanezumab 120 mg monthly and fremanezumab 225 mg monthly. The claim for safety may be reasonable noting that the trials included were not powered for the assessment of safety outcomes.

6.30 The evaluation considered the evidence for other outcomes of interest, including those achieving a 50% reduction in the number of migraine days per month and in the severity of migraine (as indicated by the HIT-6), suggest that the use of eptinezumab may achieve similar outcomes to the existing CGRP inhibitors when used in CM, with a reduced frequency of treatment administration. The ESC noted the PBAC recommended an amendment to the existing listing of fremanezumab for the continuing treatment of chronic migraine to provide patients with options of both monthly dosing and quarterly dosing at the March 2022 PBAC meeting.

6.31 The ESC considered that, on balance, the claim that eptinezumab was non-inferior to galcanezumab and fremanezumab in terms of effectiveness and safety was reasonable.

6.32 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was reasonable.

Economic analysis

6.33 The submission presented the results of a cost minimisation approach (CMA) of eptinezumab vs. galcanezumab over a three-year time horizon. The CM approach presented by the submission was consistent with that for galcanezumab versus botox (paragraph 4.4 and 5.2, galcanezumab PSD, November 2020).

6.34 The key components of the CMA are presented in Table 9.

Table 9: Key components and assumptions of the cost-minimisation analysis

Component	Claim or assumption
Therapeutic claim: effectiveness	Non-inferior to galcanezumab.
Therapeutic claim: safety	Non-inferior to galcanezumab.
Evidence base	Indirect comparison: DELIVER; PROMISE-2; Study-005 (eptinezumab versus placebo); REGAIN (galcanezumab versus placebo).
Equi-effective doses	Eptinezumab 100 mg IV injection every 12 weeks is equi-effective to: Galcanezumab 120 mg SC injection every month, with a 240 mg loading dose as the initial dose.
Costs included	Drug acquisition and administration costs.
Other costs or cost offsets	No cost offsets were claimed. The submission claimed additional costs for eptinezumab were for additional GP visits for IV infusion.

Abbreviations: IV=intravenous; SC=subcutaneous
Source: Table 98 p210 of the submission

6.35 The equi-effective doses presented by the submission were eptinezumab 100 mg q12w with galcanezumab 240 mg initially, followed by 120 mg every month. This therapeutic relativity was based on the indirect comparison of eptinezumab (PROMISE-2, Study 005, DELIVER) and galcanezumab (REGAIN, CONQUER).

6.36 The submission calculated an ex-manufacturer price for eptinezumab of $[redacted] per pack (Table 10). This was estimated based on the published approved ex-manufacturer price for galcanezumab ($498.59). The CMA presented by the submission included administration costs based on neurologist visits (MBS item 116, $79.75) and GP visits (MBS item 23, $39.10).

Table 10: Results of the cost-minimisation analysis

Row	Component	Galcanezumab	Eptinezumab	Source / calculation
A	Time horizon, years	3	3	Assumption
	Drug costs			
B	Dosing details	120 mg per month with a 240 mg loading dose as the initial dose	100 mg every 12 weeks	Product information
C	AEMP per unit	$498.59	$	PBS item 12478R / 12469G
D	Unit volume	120 mg	100 mg	
E	Units utilised over three years	37.53	13.04	Estimated [a]
F	Total drug costs	$18,709.59	$	C*E
	Medical service costs			
H	Neurologist visits	1.5[b]	1.5[c]	Estimated based on galcanezumab PSD
I	GP visits	5.25[b]	11.54[c]	
J	Cost per neurologist visit	$79.75	$79.75	MBS item 116
K	Cost per GP visit	$39.10	$39.10	MBS item 23
L	Total medical service costs	$324.90	$	H*J + I*K
	Total costs			
M	Total drug and medical service costs	$19,034.49	$	F+L

Abbreviations: AEMP= approved ex-manufacture price; GP= general practitioner; MBS= Medicare Benefits Schedule; PBS= Pharmaceutical Benefits Scheme; PSD=public summary document

Source: Table 101, p213 of the submission

Note: Numbers in italics consistent with CMA workbook supplied by the submission.

a. Galcanezumab = 365.25 / 30 * Row A + 1; Eptinezumab = 365.25 / 84 * Row A.

b. Galcanezumab no. of neurologist visit=0.5*3; no. of GP visit= 1.75*3

c. Eptinezumab no. neurologist visit=0.5*3; no. of GP visit=3.85*3

6.37 Eptinezumab is administered intravenously over 30 minutes while the MBS item for GP visit applied by the submission (MBS item 23) accounts for a visit of less than 20 minutes in duration. The evaluation tested the impact on the CMA of an alternative administration fee for GP services, using a fee for GP visits lasting at least 20 minutes (MBS item 36; $75.75). This resulted in an AEMP of $ per 100 mg vial. The PSCR sponsor acknowledged that MBS item 24 ($39.10) may not be sufficient for infusion of eptinezumab over 30 minutes, and that MBS item 36 ($75.75) is likely a more appropriate item for the costing of GP visits for eptinezumab administration.

6.38 The submission did not present a CMA comparing eptinezumab with fremanezumab. The submission stated that galcanezumab and fremanezumab were both cost-minimised to botox, and effectively cost-minimised to one another; therefore, the CMA should result in the same price for eptinezumab against fremanezumab. During the evaluation the cost-minimised price per pack of eptinezumab was re-calculated using the price for fremanezumab and assuming equi-effective doses of eptinezumab 100 mg q12w and fremanezumab 225 mg every month. The revised price cost-minimised to fremanezumab over a three- year treatment period was $ (using the published price of fremanezumab and MBS item 23 for administration as applied in the submission).

Drug cost/patient/year

6.39 Using the price calculated in the submission, the dispensed cost per pack of eptinezumab 100 mg (12 weeks treatment) was $. Assuming 4.35 doses per patient (365.25/84) per year are dispensed the cost would be $ per patient. The estimated costs per patient for eptinezumab and galcanezumab are presented in Table 11.

Table 11: Drug cost per patient for eptinezumab and galcanezumab

	Eptinezumab		Galcanezumab	
	Cost-minimisation analysis (based on ex-manufacturer prices)	**Financial estimates (based on dispensed prices)**	**Cost-minimisation analysis (based on ex-manufacturer prices)**	**Financial estimates (based on dispensed prices)**
Dose	100 mg q12w	100 mg q12w	240 mg loading dose then 120 mg q4w	120 mg q4w
Treatment duration[a]	3 years[b]	12 months for responders[c]	3 years[b]	12 months for responders[c]
Number of injections	13.04[d]	4.35[e]	37.53[f]	12.18[g]
Drug cost per injection	$	$	$498.59	$559.02
Cost/patient/year	$	$	$6,569	$6,809

Abbreviations; AEMP= approved ex-manufacturer price; DPMQ=dispensed price for maximum quantity mg = milligram; NA = not applicable; q12w= every 12 weeks; q4w= every 4 weeks/monthly

Source: compiled during the evaluation

a. Treatment duration in the clinical trials was 12 weeks.
b. Duration of treatment is based on galcanezumab PSD i.e. 3 years (paragraph 4.4, galcanezumab PSD, November 2020).
c. Assuming 4.35 doses per year (365.25/84) for eptinezumab and 12.18 doses per year for galcanezumab (365.25/30)
d. (365.25/84)*3
e. 365.25/84
f. (12.18*3)+1
g. Assuming 12.18 doses per year for ongoing responders (i.e., no loading dose)
h. Different to the requested published DPMQ in paragraph 3.1

Estimated PBS usage & financial implications

6.40 This submission was not considered by DUSC.

6.41 The submission adopted an epidemiological approach in estimating the potential utilisation of eptinezumab on the PBS. The submission justified not adopting a market share approach on the basis of the recency of listing (June-August 2021) for the two other CGRP inhibitors but noted that uptake to date has been higher than anticipated.

6.42 The key inputs informing the financial estimates presented by the submission are presented in Table 12. The submission applied the assumptions from the budget impact model presented in the galcanezumab November 2020 submission (paragraph 4.15 and paragraph 5.8, galcanezumab PSD, November 2020). These assumptions were previously accepted by the PBAC, and subsequently used to inform the expenditure caps for a risk sharing agreement (RSA) for galcanezumab. Galcanezumab was the first CGRP inhibitor listed on the PBS.

Table 12: Key inputs for financial estimates

Parameter	Value applied	Comment/ Source
Prevalent population	14.65%	Assumption (paragraph 4.15, galcanezumab PSD, November 2020)
Prevalence of chronic migraine	10%	
Failed 3 or more prior treatments	12%	
Uptake rate in the prevalent pool, %	Yr 1: 12.5% Yr 2: 10% Yr 3: 7.5% Yr 4: 5% Yr 5: 0% Yr 6: 0%	Assumption. The submission assumed 90% of eligible patients would use CGRP inhibitors. This was applied as 40% uptake in 2021, decreasing to 15% in 2022, and then decreasing linearly by 2.5% each year until 0% in Year5 and Year 6 of funding. No justification for these assumptions was provided.
Uptake rate in the incident pool, %	90%	Assumption. The submission assumed the uptake rate was reasonable given higher than expected uptake of galcanezumab and fremanezumab based on the PBS utilisation data.
Treatment responders: proportion of patients achieve a 50% reduction in migraine headache days at Week 12	40%	Assumption (paragraph 5.8, galcanezumab PSD, November 2020)
Annual persistence: proportion of responding patients continuing treatment each subsequent year	95%	
Proportion 1L non-responders receiving a 2nd CGRP inhibitor, and 2L non-responders receiving a 3rd CGRP inhibitor.	80%	Assumption. The submission has not provided justification for this estimate.
Eptinezumab market share	1L: [redacted]% in Yr 1; [redacted]% in Yr 6 2L: [redacted]% in Yr 1, [redacted]% in Yr 6 3L: [redacted]% in Yr 1, [redacted]% in Yr 6[a]	Assumptions. Assumption Estimated during the evaluation based on the submission
MBS costs	MBS item 116: Neurologist visit $79.75 MBS item 23: GP visits $39.10	The MBS fees applied by the submission are likely to be inappropriate for the intravenous administration of eptinezumab. Eptinezumab is administered intravenously over 30 min while the MBS item for GP visit applied by the submission accounts for a visit of less than 20 min in duration. The evaluation considered that MBS item 36 (professional attendance by a general practitioner lasting at least 20 minutes) may be more appropriate in this context. The results of a sensitivity analysis using MBS item 36 to account the GP visits was conducted during the evaluation.

Abbreviations: AEMP= approved ex-manufacture price CGRP= calcitonin gene-related peptide; CMA=cost-minimisation analysis; DPMQ= dispensed price per maximum quantity; GP= general practitioner; MBS= Medicare Benefits Schedule; PSD=public summary document; 1L-first line; 2L=second line.

Source: Table 4.1.1 of the evaluation

Note: a. Estimated during the evaluation based on total estimated use of eptinezumab in the 3L setting as a proportion of total eptinezumab use.

6.43 For the epidemiological approach, the submission assumed a total of 90% of prevalent eligible patients will use a CGRP inhibitor over the first six years of listing eptinezumab (applied as 40% uptake in 2021, decreasing to 15% in 2022, and then decreasing linearly by 2.5% each year until 0% in Year 5 and Year 6 of funding), with a 90% uptake rate among the incident patients in the year of incidence. The submission assumed 80% of patients who don't respond to treatment in 1L will receive treatment with a different CGRP in 2L treatment, with a 95% persistence rate (i.e. proportion of

respondents on treatment in 2L and 3L of treatment each subsequent year). The assumed uptake of 80% in the 2L treatment setting is uncertain as no data for the sequential use of CGRP inhibitors was presented by the submission. This may have overestimated the total utilisation of CGRP inhibitors (eptinezumab, galcanezumab and fremanezumab).

6.44 Thus, the approach in the submission assumed sequential use of the available CGRP inhibitors and that in addition to displacing a proportion of use of galcanezumab and fremanezumab in the 1L and 2L settings, eptinezumab listing would result in use in the 3L setting, projected to increase the total utilisation of CGRP inhibitors. The submission applied the changes in the estimated number of patients initiating subsequent lines of treatment after 1 year. This assumed that patients would not commence their next line of therapy within their first year of treatment, i.e. assuming that the treatment benefit lasts for one year.

6.45 The application of the submission's assumed uptake of sequential use should have resulted in 23% of patients commencing 3L therapy in the first year (estimated number of eligible patients, 60% non-response rate to previous lines of therapy, with 80% uptake of the next line of therapy - such that 48% of patients commence 2L therapy, with 3L use occurring among 48% x 60% x 80% = 23%). However, the estimates provided by the submission show that 3L use was 83% of total use in year 1. This suggests that the submission may have overestimated the extent of use in the 3L setting.

6.46 The estimated total number of patients on treatment each year was adjusted for response and treatment continuation in each year of funding. A summary of the estimated use and financial implications for the PBS of listing eptinezumab for the treatment of CM is presented in Table 13.

Table 13: Estimated use and financial implications of eptinezumab listing (using published prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use (number of scripts dispensed)						
Eptinezumab	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Galcanezumab	-[redacted][2]	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]
Fremanezumab	-[redacted][2]	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]
Estimated cost of eptinezumab (world with eptinezumab)						
Cost to PBS/RPBS less co-payments	$[redacted][4]	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Estimated cost of galcanezumab and fremanezumab (world with eptinezumab)						
Cost to PBS/RPBS less co-payments	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][4]	-$[redacted][6]	-$[redacted][6]
Net cost to PBS	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**	**$[redacted][4]**

Abbreviations: PBS=Pharmaceutical Benefits Scheme; RPBS=Repatriation Pharmaceutical Benefits Scheme
Source: Table 122, p235 of the submission, Table 112, p225 of the submission, Section 4 Workbook
The redacted values correspond to the following ranges:
[1] *10,000 to < 20,000*
[2] *500 to < 5,000*
[3] *5,000 to < 10,000*
[4] *$10 million to < $20 million*
[5] *$20 million to < $30 million*
[6] *$0 to < $10 million*

6.47 The estimated net cost to Government for the first 6 years of eptinezumab listing was $10 million to < $20 million in Year 1 and $10 million to < $20 million in Year 6 of listing (based on published prices). The estimate was sensitive to the uptake rate among eligible patients and changes in the number of lines of treatments and the proportion of non-respondents receiving subsequent line of treatment.

6.48 The submission presented results of sensitivity analyses assuming no sequential use and assuming no sequential use beyond 2 lines of therapy. The results showed a reduction in total estimated expenditure over six years when sequential use of GCRP inhibitors is removed. Removing sequential use reduced the net impact to $10 million to < $20 million in Year 6. The PBAC noted data provided by the DUSC Secretariat indicated that only a small proportion (< 10%) of patients are currently using sequential treatment and it is unclear if patients are switching due to non-response or tolerability issues.

6.49 The submission has not allowed for the possibility that eptinezumab will be used for the treatment of patients with episodic migraine. While the TGA registered indication and proposed PBS listing for eptinezumab is for use in patients with CM, the recent positive recommendation from the PBAC for the use of galcanezumab in patients with EM increases the potential for the use of eptinezumab in that same patient group (potentially following galcanezumab). The PSCR stated the sponsor is open to the suggestion of expanding the indication to allow use of eptinezumab for patients with >8 migraine headache days per month, as has been recently recommended by the PBAC for galcanezumab and noted the results for the treatment resistant high frequency episodic migraine subgroup for eptinezumab from the DELIVER trial was provided in the submission. The ESC noted listing for the episodic migraine population would require a submission to the PBAC.

Quality Use of Medicines

6.50 The submission stated that the sponsor is training nursing staff on the dilution and administration of eptinezumab where appropriate via in-service training sessions and also by means of the provision of material. This includes material such as a step-by-step administration video and storage posters which were developed in collaboration with nurses.

Financial Management – Risk Sharing Arrangements

6.51 The submission requested that eptinezumab be included in the risk sharing arrangement (RSA) for the existing CGRP inhibitors. The submission acknowledged the uncertainty related to the sequential use of GCRP inhibitors as no evidence demonstrating the clinical and cost-effectiveness of sequential use for eptinezumab was presented. To alleviate this uncertainty and to ensure the PBS listing is cost neutral to the PBS without excluding sequential use, the submission proposed eptinezumab would join the existing CGRP inhibitors expenditure caps.

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

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required (Streamlined) listing of eptinezumab for the treatment of chronic migraine in patients who have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of eptinezumab would be acceptable if it were cost-minimised against the lowest cost alternative. The PBAC considered it was appropriate for eptinezumab to be added to the current risk sharing arrangement for this class of medicines with no increase in expenditure caps.

7.2 The PBAC noted galcanezumab and fremanezumab were alternative therapies to eptinezumab and the equi-effective doses were:

eptinezumab 100 mg every 12 weeks = galcanezumab 240 mg initially then 120 mg every month = fremanezumab 225 mg every month.

7.3 The PBAC noted the consumer comments and acknowledged there was a clinical need for access to additional calcitonin gene-related peptide (CGRP) inhibitors to increase the treatment options for people with chronic migraine.

7.4 The PBAC noted the submission provided clinical evidence for eptinezumab versus placebo from three randomised controlled trials (DELIVER, Study 005 and PROMISE-2). The PBAC considered the two subgroups of patients in the DELIVER study with chronic migraine who had failed 2 to 4 (n=405) or ≥ 3 (n=166) prior preventative therapies were the most applicable for the requested PBS listing. The PBAC considered that eptinezumab resulted in a clinically significant reduction in the number of the monthly migraine days (MMD) compared to placebo, with a reduction of 3.3 (95% CI: -4.5. -2.0) and 4.4 (95% CI: -7.15, -1.65) MMD at 12 weeks in chronic migraine patient with 2 to 4 or ≥3 prior treatment failures, respectively.

7.5 The PBAC noted the submission presented an indirect treatment comparison (using placebo as the common comparator) to support the clinical claim that eptinezumab was non-inferior to galcanezumab and fremanezumab in terms of effectiveness and safety. The PBAC noted there was no statistically significant difference in the reduction in number of MMD from baseline between eptinezumab and galcanezumab and between eptinezumab and fremanezumab for patients with chronic migraine with 2 to 4 preventative treatment failures. However, the upper 95% confidence interval of the difference exceeded the nominated MCID of 2 days (3.25 for comparison with galcanezumab and 2.67 for comparison with fremanezumab). Similarly, the PBAC noted there was no statistically significant difference in the reduction of MMD between eptinezumab and galcanezumab for patients with chronic migraine with ≥ 3 preventative treatment failures but the upper 95% confidence interval of the difference exceeded the MCID (4.16). However, the PBAC considered that, on balance, the claim that eptinezumab is non-inferior to galcanezumab and fremanezumab in terms of effectiveness was reasonably supported by the data presented.

7.6 The PBAC considered the claim that eptinezumab is non-inferior to galcanezumab and fremanezumab in terms of safety was reasonably supported by the data presented.

7.7 The PBAC considered the methodology for the CMA presented in the submission was reasonable but should include MBS item 36 for the cost of eptinezumab administration as discussed in paragraph 6.37.

7.8 The PBAC considered the submission overestimated the extent of sequential use of the CGRP inhibitors which overestimated the net cost of listing eptinezumab on the PBS for chronic migraine. The PBAC considered that, given its recommendation was on a cost minimisation basis to the least costly alternative CGRP inhibitor, the listing of eptinezumab for chronic migraine on this basis was likely to be cost neutral. The PBAC considered it was appropriate for eptinezumab to be added to the risk sharing arrangement in place for galcanezumab and fremanezumab with no increase in expenditure caps.

7.9 The PBAC considered the administration of eptinezumab could be appropriately managed in the community setting and a General Schedule listing was reasonable.

7.10 The PBAC did not recommend removal of the clinical criteria 'Patient must continue to be appropriately managed for medication overuse headache'. The PBAC considered this criteria was unlikely to be limiting patient access and was clinically appropriate.

7.11 The PBAC considered the restriction criteria for eptinezumab should be consistent with the criteria for galcanezumab and fremanezumab with the addition of the administrative note 'Eptinezumab at a dose of 300 mg, once every twelve weeks, is not subsidised on the PBS'.

7.12 The PBAC recommended that eptinezumab should be treated as interchangeable on an individual patient basis with galcanezumab and fremanezumab.

7.13 The PBAC advised that eptinezumab is not suitable for prescribing by nurse practitioners.

7.14 The PBAC noted that this submission is not eligible for an Independent Review.

7.15 The PBAC recommended that the Early Supply Rule should apply.

7.16 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because eptinezumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over galcanezumab or fremanezumab, or not expected to address a high and urgent unmet clinical need given the presence of alternative therapies, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
EPTINEZUMAB					
100mg vial for intravenous infusion	NEW	1	1	0	Vypeti
Restriction Summary new (variant of 12028)/ Treatment of Concept: new (variant of 12064)					
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)				
	Prescriber type: ☒Medical Practitioners				
	Restriction type: ☒Authority Required (Streamlined) [new/existing code]				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	Episodicity: Chronic				
	Severity:				
	Condition: Migraine				
	Indication: Chronic migraine				
	Treatment Phase: Initial treatment				
	Treatment criteria:				
	Must be treated by a neurologist				
	AND				
	Treatment criteria:				
	Patient must not be undergoing concurrent treatment with the following PBS benefits: (i) botulinum toxin type A listed for this PBS indication, (ii) another drug in the same pharmacological class as this drug listed for this PBS indication				
	AND				
	Clinical criteria:				
	Patient must have experienced an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months, prior to commencement of treatment with this medicine for this condition				
	AND				
	Clinical criteria:				
	Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with this drug for this condition				
	AND				
	Clinical criteria:				
	Patient must be appropriately managed by his or her practitioner for medication overuse headache, prior to initiation of treatment with this drug.				
	AND				
	Population criteria:				
	Patient must be aged 18 years or older				

	Prescribing Instructions: Prophylactic migraine medications are propranolol, amitriptyline, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate or topiramate.
	Prescribing Instructions: Patient must have the number of migraine days per month documented in their medical records.
	Administrative note: Eptinezumab at a dose of 300 mg, once every twelve weeks, is not subsidised on the PBS.

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
EPTINEZUMAB					
100mg vial for intravenous infusion	NEW	1	1	1	Vypeti

Restriction Summary new (variant of 12028)/ Treatment of Concept: new (variant of 12064)	
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (Streamlined) [new/existing code]
	Administrative Advice: *No* increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Episodicity: Chronic
	Severity:
	Condition: Migraine
	Indication: Chronic migraine
	Treatment Phase: Continuing treatment
	Treatment criteria:
	Must be treated by a specialist neurologist or in consultation with a specialist neurologist
	AND
	Treatment criteria:
	Patient must not be undergoing concurrent treatment with the following PBS benefits: (i) botulinum toxin type A listed for this PBS indication, (ii) another drug in the same pharmacological class as this drug listed for this PBS indication
	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine days per month
	Clinical criteria:
	Patient must continue to be appropriately managed for medication overuse headache
	Prescribing Instructions: Patient must have the number of migraine days per month documented in their medical records.
	Administrative note: Eptinezumab at a dose of 300 mg, once every twelve weeks, is not subsidised on the PBS.

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

9 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.

10 Sponsor's Comment

Lundbeck Australia is very pleased that Vyepti® (eptinezumab) has been recommended for listing on the Pharmaceutical Benefits Scheme (PBS), allowing patients an intravenous treatment option for the prevention of chronic migraine. Lundbeck will now work with the Department of Health to make Vyepti available on the PBS as soon as possible.