

## 7.05 GALCANEZUMAB, Injection 120 mg in 1 mL pre-filled pen, Emgality<sup>®</sup>, Eli Lilly Australia Pty Ltd.

### 1 Purpose of submission

- 1.1 The standard re-entry submission requested an amendment to the current galcanezumab chronic migraine listing to include patients with high frequency episodic migraine (defined as 8 to <15 migraine headache days per month with <15 headache days) who have an inadequate response, intolerance, or a contraindication to at least three prophylactic migraine medications.
- 1.2 The listing was requested on the basis of a cost-utility analysis versus placebo/best supportive care. The key components of the clinical issue addressed in the resubmission are presented in the table below.

**Table 1: Key components of the clinical issue addressed in the resubmission**

Component	Description
Population	Adult patients with <u>high frequency episodic migraine, defined as 8 to &lt;15 migraine headache days per month with &lt;15 headache days per month</u> , who have an inadequate response, intolerance or a contraindication to at least three prior prophylactic migraine medications.
Intervention	Galcanezumab 120 mg injected subcutaneously once monthly, with a 240 mg loading dose as the initial dose.
Comparator	Best supportive care
Outcomes	Reduction in number of migraine headache days, proportion of patients achieving 50% reduction in monthly migraine headache days, monthly headache days, quality of life.
Clinical claim	In patients with treatment-resistant <u>high frequency episodic migraine</u> , galcanezumab is superior to best supportive care in terms of efficacy and similar in terms of safety.

Source: Table 1.2.1, p29 of the resubmission.

Underlined text indicates key changes from the November 2020 submission.

### 2 Background

#### **Registration status**

- 2.1 Galcanezumab was registered by the TGA on 29 May 2019 for the prophylaxis of migraine in adults.

#### **Previous PBAC consideration**

- 2.2 The matters of concern from the November 2020 PBAC meeting are summarised in the table below.

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Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Proposed restriction	The PBAC considered episodic and chronic migraine are on a continuum, and patients may cycle between the two, rather than discrete clinical entities for the purpose of PBS listing. The PBAC considered a single listing for treatment-resistant migraine would be a more reasonable approach (para 7.3, galcanezumab PSD, November 2020 PBAC meeting).	The resubmission proposed a single migraine listing that included patients with treatment-resistant chronic and episodic migraine.
Requested price	The PBAC noted the price requested for episodic migraine was higher than the price recommended by the PBAC for chronic migraine in July 2019 and considered this was not adequately justified in the submission, noting that the magnitude of benefit provided by galcanezumab is likely to be less for episodic migraine than for chronic migraine (para 7.7, galcanezumab PSD, November 2020 PBAC meeting).	The proposed effective ex-manufacturer price (\$████) was lower than the effective ex-manufacturer price proposed in the November 2020 episodic migraine submission (\$████) but remained higher than the effective price of galcanezumab under the chronic migraine PBS listing (\$████).
Clinical evidence	The PBAC previously noted that treatment with galcanezumab resulted in a clinically significant reduction in the number of migraine headache days compared to placebo, with a reduction of 2 to 6 migraine headache days, depending on the patient population, from a baseline of approximately 20 (para 7.3, galcanezumab PSD, July 2019 PBAC meeting). The PBAC previously considered that treatment with galcanezumab resulted in a modest reduction in the number of migraine headache days compared to placebo (para 7.5, galcanezumab PSD, November 2020 PBAC meeting). The PBAC noted the average number of migraine headache days per month at baseline in the subgroup of patients with treatment-resistant episodic migraine was 10 and considered the magnitude of benefit observed in the CONQUER trial (i.e., reduction in migraine headache days per months of ~3) may not be achieved in the PBS population who are required to have 4 or more migraine headache days per month (para 7.6, galcanezumab PSD, November 2020 PBAC meeting).	The resubmission was based on the results for the subgroup of patients with 'high frequency' episodic migraine, defined in the resubmission as 8 to 14 monthly migraine days.
Economic model	The ESC considered application of higher utilities to the galcanezumab 'on-treatment' health state was not adequately justified, and the model was sensitive to the use of these utilities (para 6.51, galcanezumab PSD, November 2020 PBAC meeting).	The resubmission included additional evidence from a correlation analysis to support the inclusion of the 'on treatment' health state utilities.
	The ESC considered that the maintenance of the galcanezumab treatment response over the 5-year model time horizon was a highly optimistic assumption (para 6.60, galcanezumab PSD, November 2020 PBAC meeting).	The resubmission presented a summary of available long-term effectiveness studies for galcanezumab and other CGRP inhibitors to support the maintenance of the galcanezumab treatment response.
	The ESC was of the view that the model presented in the submission had significant issues, incorporating numerous optimistic data assumptions and structural assumptions that mean it is unlikely to be reliable for decision making (para 6.60, galcanezumab PSD, November 2020 PBAC meeting).	The structure of the economic model was unchanged from the November 2020 submission. Model inputs were updated to reflect the characteristics and results for the CONQUER trial high frequency episodic migraine with ≥3 prior treatment failures subgroup.

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Component	Matter of concern	How the resubmission addresses it
	The PBAC noted the significant issues associated with the economic model (para 6.60) but considered galcanezumab is not cost-effective for episodic migraine at the price requested in the submission (para 7.7, galcanezumab PSD, November 2020 PBAC meeting).	The proposed effective AEMP was reduced from \$█ to \$█. The resubmission proposed a RSA with combined caps for chronic migraine and high frequency episodic migraine.
Financial estimates	The PBAC noted the estimated cost of listing galcanezumab on the PBS for episodic migraine was high and uncertain. The PBAC considered the estimate that 2.3% of patients with migraine would be eligible for treatment with galcanezumab if it was listed for episodic migraine was poorly supported and highly uncertain (para 7.8, galcanezumab PSD, November 2020 PBAC meeting). The PBAC advised any resubmission for episodic migraine should provide revised financial estimates, accounting for patients that may already have been attributed to the chronic migraine population (para 7.9, galcanezumab PSD, November 2020 PBAC meeting).	The resubmission provided updated financial estimates. The assumed migraine prevalence was increased 14.5% to 22.8%. Other epidemiological inputs were updated based on the results of a clinician survey commissioned by the sponsor. The galcanezumab uptake rates were updated, with lower uptake assumed in Year 1, and higher uptake assumed for Years 2 to 6.

Source: Galcanezumab, Public Summary Document, November 2020 PBAC meeting.

Abbreviations: AEMP, approved ex-manufacturer price; PSD, public summary document; RSA, risk-sharing arrangement

2.3 Galcanezumab is currently listed on the PBS for treatment-resistant chronic migraine (patients experiencing an average of 15 or more headache days per month, with at least 8 days of migraine).

### 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 (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
<b>Initial</b>					
GALCANEZUMAB 120 mg / 1 mL solution for injection, pre-filled pen	2	2	1	\$1110.96 (published) \$█ (effective)	Emgality®, Eli Lilly Australia Pty Ltd
<b>Continuing</b>					
GALCANEZUMAB 120 mg / 1 mL solution for injection, pre-filled pen	1	1	5	\$569.96 (published) \$█ (effective)	Emgality®, Eli Lilly Australia Pty Ltd

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<b>Category / Program:</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	Medical Practitioners
<b>Condition:</b>	Treatment-resistant migraine
<b>Restriction:</b>	Streamlined
<b>Treatment phase:</b>	Initial
<b>Treatment criteria:</b>	Must be treated by a neurologist. <i>AND</i> <i>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</i>
<b>Clinical criteria:</b>	Patient must have experienced at least 8 days of migraine per month, over a period of at least 6 months, prior to commencement of treatment with this medicine for this condition, <i>AND</i> 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 medicine for this condition, <i>AND</i> Patient must be appropriately managed for medication overuse headache, prior to initiation of treatment with this medicine for this condition <del><i>AND</i> Patient must not have previously received PBS-subsidised treatment with this drug for this condition</del>
<b>Population criteria:</b>	Patient must be aged 18 years or older.
<b>Prescriber Instructions:</b>	Prophylactic migraine medications are propranolol, amitriptyline, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate or topiramate. Patient must have a baseline measurement of the number of migraine days per month documented in their medical records.
<b>Treatment phase:</b>	Continuing
<b>Treatment criteria:</b>	Must be treated by a specialist neurologist or in consultation with a specialist neurologist. <i>AND</i> <i>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</i>
<b>Clinical criteria:</b>	Patient must have previously received PBS-subsidised treatment with this drug for this condition <i>AND</i> Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine headache days per month <i>AND</i> Patient must continue to be appropriately managed for medication overuse headache
<b>Treatment phase:</b>	<del>Grandfathered</del>
<b>Treatment criteria:</b>	<del>Must be treated by a specialist neurologist or in consultation with a specialist neurologist.</del>

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<b>Clinical criteria:</b>	<p>Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]</p> <p>AND</p> <p>Patient must have experienced at least 8 days of migraine per month, over a period of at least 6 months, prior to commencement of treatment with this drug for this condition</p> <p>AND</p> <p>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</p> <p>AND</p> <p>Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine days per month</p> <p>AND</p> <p>Patient must continue to be appropriately managed for medication overuse headache</p>
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Source: Table 1.5.1, pp36-37; Table 1.5.2, p38; Table 1.5.3, p39; Table 1.5.4, p39 of the resubmission.

- 3.2 The resubmission requested a special pricing arrangement (SPA).
- 3.3 The proposed effective ex-manufacturer price (\$████) was lower than the effective ex-manufacturer price proposed in the November 2020 episodic migraine submission (\$), but higher than the effective price of galcanezumab under the chronic migraine PBS listing (\$). The PBAC previously noted the price requested for episodic migraine was higher than the price recommended by the PBAC for chronic migraine in July 2019 and considered this was not adequately justified in the submission, noting that the magnitude of benefit provided by galcanezumab is likely to be less for episodic migraine than for chronic migraine (para 7.7, galcanezumab Public Summary Document [PSD], November 2020 PBAC meeting).
- 3.4 The proposed restriction includes patients with treatment-resistant chronic and high frequency episodic migraine and would replace the current treatment-resistant chronic migraine listing.
- 3.5 The PBAC considered it would be appropriate to specify ‘migraine headache days’ (rather than ‘migraine days’) in order to align with the definitions used in the CONQUER trial.
- 3.6 The PBAC considered it would be appropriate to amend the treatment criteria in the continuing restriction “Must be treated by a specialist neurologist or in consultation with a specialist neurologist” to “Must be treated by a neurologist or in consultation with a neurologist” to be consistent with the terminology used in the initial restriction criteria.
- 3.7 Consistent with the current chronic migraine PBS listing, the proposed continuing treatment restriction specifies that patients must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine headache days per month.
- 3.8 The resubmission proposed an Authority Required (Streamlined) general schedule listing of galcanezumab for the grandfathered treatment of patients receiving galcanezumab under the sponsor’s special access program. The resubmission estimated that < 500 patients would be eligible for grandfathered treatment based on

the proposed PBS listing criteria. The PBAC noted a separate restriction to allow transition to PBS-subsidised treatment would not be required with the proposed wording above.

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

## **4 Population and disease**

- 4.1 Migraine is a disabling primary headache disorder characterised by recurrent headaches of moderate to severe intensity, which tend to be aggravated by routine physical activity, and are often associated with nausea, photophobia and phonophobia. Approximately 90% of migraine patients have moderate or severe pain and have a reduced ability to function during the headache attacks, with one-third requiring bed rest during their attacks (Lipton et al., 2007). Migraine episodes can also significantly impair functional ability at work or school, at home, and in social situations (American Headache Society Consensus Statement, 2018).
- 4.2 The resubmission positioned galcanezumab as an alternative to best supportive care for use in patients with treatment-resistant high-frequency episodic migraine, defined in the resubmission as patients with 8 to 14 migraine headache days per month with <15 monthly headache days, who have an inadequate response, intolerance or contraindication to at least three prophylactic migraine medications. The November 2020 submission targeted a broader population of patients with episodic migraine, based on 4 to 14 monthly migraine days.
- 4.3 Galcanezumab is administered by subcutaneous injection using a pre-filled pen device which is suitable for patient self-administration. Following an initial loading dose of 240 mg, the recommended dose of galcanezumab is 120 mg once a month.

## **5 Comparator**

- 5.1 The resubmission nominated best supportive care as the main comparator. The PBAC previously considered that best supportive care was an appropriate comparator for patients with episodic migraine who have failed at least three prophylactic migraine medications (para 7.4, galcanezumab PSD, November 2020 PBAC meeting).

## **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 (30) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the benefit of treatment with galcanezumab including reduction in number and severity of migraines, reduced use of acute medications, improvement in quality of life and the

ability to self-administer. The comments included a number of requests for GP prescribing to improve access, noting the challenges with securing appointments with neurologists.

- 6.3 The PBAC noted the advice received from Migraine & Headache Australia that the disease burden for patients with high frequency episodic migraine is very similar to that of patients with chronic migraine. The advice noted the devastating impacts on quality of life, ability to work and livelihood for people living with migraine and the significant benefits of treatment with the CGRP antibodies.
- 6.4 The PBAC noted the support from Migraine Australia for a single PBS listing for treatment resistant migraine, rather than separate listings for high frequency episodic and chronic migraine.

### ***Clinical trial***

- 6.5 The resubmission was based on one head-to-head randomised trial (CONQUER), which compared galcanezumab 120 mg once monthly or placebo, in patients with chronic or episodic migraine, who had previously failed 2 to 4 preventive migraine treatments. The CONQUER trial was previously considered by the PBAC as part of the July 2019 and November 2020 galcanezumab submissions.
- 6.6 Details of the trial presented in the resubmission are provided in the table below.

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**Table 3: Trials and associated reports presented in the resubmission**

Trial ID	Protocol title/ Publication title	Publication citation
CONQUER (NCT03559257)	A randomized, double-blind, placebo-controlled study of galcanezumab in adults with treatment-resistant migraine – the CONQUER study. Final results from the double-blind treatment phase and interim results from the open-label treatment phase.	Clinical study report, September 2019.
	A randomized, double-blind, placebo-controlled study of galcanezumab in adults with treatment-resistant migraine – the CONQUER study. Final results from the open-label treatment phase.	Clinical study report addendum, December 2019.
	Mulleners W, Kim B, Lainez, MJ, Lanteri-Minet M et al. A phase 3 placebo-controlled study of galcanezumab in patients with treatment-resistant migraine: Results from the 3-month double-blind treatment phase of the CONQUER study.	<i>Journal of the Neurological Sciences</i> 2019; 405 (Supplement):128.
	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.	<i>Journal of the Neurological Sciences</i> 2019; 405 (Supplement):129-130.
	Ailani, J, Kuruppu D, Rettiganti M, Oakes T et al. Does wearing off of efficacy occur in galcanezumab-treated patients at the end of the monthly treatment cycle: A post-hoc analysis of four phase 3 randomized trials.	<i>Headache</i> 2021; 61 (SUPPL 1):153-154.
	Okonkwo R, Tockhorn-Heidenreich A, Stroud C, Paget MA et al. Efficacy of galcanezumab in patients with migraine and history of failure to 3-4 preventive medication categories: subgroup results from CONQUER study.	<i>Journal of Headache and Pain</i> 2021; 22(1).
	Schwedt TJ, Kuruppu DK, Dong Y, Standley K et al. Early onset of effect following galcanezumab treatment in patients with previous preventative medication failures.	<i>Journal of Headache and Pain</i> 2021; 22(1):15.
	Reuter U, Lucas C, Dolezil D, Hand AL et al. Galcanezumab in patients with multiple previous migraine preventive medication category failures: results from the open-label period of the CONQUER trial.	<i>Adv Ther.</i> 2021; 38(11):5465-5483.

Source: Table 2.3.1, pp47-49 of the resubmission.

6.7 The key features of the CONQUER randomised trial and CONQUER trial subgroup forming the basis of the resubmission are presented in the table below.

**Table 4: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome	Use in modelled evaluation
<b>Galcanezumab versus placebo</b>						
CONQUER	462	Randomised, double blinded, multi centre, (12 weeks with 12-week open-label extension)	Low	- ≥4 migraine headache days per month - 2 to 4 prior treatment failures	Change from baseline in monthly migraine headache days	≥50% responder for change in migraine days; change from baseline in monthly migraine headache days
CONQUER (high frequency episodic migraine subgroup)	80		High	- 8 to 14 monthly migraine headache days per month - 3 to 4 prior treatment failures		

Source: Table 1, pp1-2 of Attachment 3.1 of the resubmission; Table 2.5.3, p55; Table 2.5.5, pp57-59 of the resubmission.

6.8 Chronic migraine was defined in the CONQUER trial as having at least 8 migraine headache days and at least 15 headache days per 30-day period in the baseline period. Migraine headache days counted towards headache days. Episodic migraine was

defined as having fewer than 15 headache days per 30-day period in the baseline period.

- 6.9 The CONQUER trial included a four-week baseline period, which required patients to comply with a headache diary. It is unclear how the efficacy results from these trials would apply to those who did not comply with a headache diary. For example, if the non-compliers were different from the compliers who initiated the randomised phase and these differences affect the treatment effect estimates, then the trial results cannot be generalised.
- 6.10 Patients in the trial were permitted to use acute medicines for the treatment of migraines, however, they were not permitted to use them in a prophylactic manner. Patients were not permitted to use any other prophylactic medications during the trial. This may not reflect the management of patients in the PBS population.
- 6.11 A list of the CONQUER trial subgroups included in the resubmission is presented in the table below.

**Table 5: CONQUER trial subgroups included in the resubmission**

CONQUER trial population	Number of prior treatments	Included migraine subtypes
ITT population	2 to 4	Chronic + episodic
Episodic migraine subgroup	2 to 4	Episodic
Episodic migraine subgroup with $\geq 3$ prior treatments	3 to 4	Episodic
High frequency episodic migraine subgroup	2 to 4	Episodic
High frequency episodic migraine subgroup with $\geq 3$ prior treatments	3 to 4	Episodic

Source: Section 2.6, pp60-69; Section 2.7, pp69-76 of the resubmission; Attachment 3.1, pp5-7 of the resubmission.

Blue shading indicates CONQUER trial populations presented in the November 2020 galcanezumab submission

- 6.12 Results for the high frequency episodic migraine subgroups presented in the resubmission were based on post hoc analyses and were at high risk of bias.
- 6.13 As in the November 2020 galcanezumab episodic migraine submission, data from the EVOLVE and CGAJ trials were used to inform aspects of the economic model (EVOLVE trials: the distribution of monthly migraine days and duration of waning treatment effect following galcanezumab discontinuation; CGAJ: galcanezumab treatment discontinuation rates).

### **Comparative effectiveness**

- 6.14 Results for the CONQUER ITT population and the ITT episodic migraine subpopulation are presented in the table below. The results are unchanged from the November 2020 submission.

Table 6: ITT population and episodic migraine subpopulation results for CONQUER trial

	Galcanezumab		Placebo		LS mean change difference (95% CI)
	N	Mean days (SE)	N	Mean days (SE)	
<b>Change from baseline in number of monthly migraine headache days</b>					
<b>Double blind treatment phase (12 weeks; galcanezumab versus placebo)</b>					
ITT population	230	-4.14 (0.32)	228	-1.02 (0.32)	-3.12 (-3.92, -2.32)
ITT episodic subpopulation	137	-2.88 (0.34)	132	-0.31 (0.34)	-2.57 (-3.41, -1.72)
	Galcanezumab		Placebo		OR (95%CI)
	Model estimated rate (SE)		Model estimated rate (SE)		
<b>Estimated proportion of ≥50%, ≥75% and 100% responders for migraine headache days</b>					
<b>ITT population</b>					
≥50% responders	37.7 (2.5)		13.3 (1.8)		<b>3.94 (2.72, 5.69)</b>
≥75% responders	14.5 (2.0)		3.3 (1.1)		<b>5.01 (2.35, 10.68)</b>
100% responders	4.9 (1.4)		0		NE
<b>Episodic migraine subpopulation</b>					
≥50% responders	41.8 (3.2)		17.1 (2.5)		<b>3.48 (2.25, 5.38)</b>
≥75% responders	18.4 (2.5)		3.7 (1.5)		<b>5.88 (2.37, 14.55)</b>
100% responders	7.7 (1.9)		0		NE
≥30% responders	60.7 (NR)		32.5 (NR)		NR

Source: Table 4, pp5-6; Table 5, p6 of Attachment 3.1 of the resubmission; Table CGAJ.11.4, p102 of the CONQUER clinical study report. Abbreviations: CI, confidence interval; ITT, intention to treat; LS, least squares; NE, not estimable; NR, not reported; OR, odds ratio; SE, standard error.

- 6.15 Treatment with galcanezumab was associated with a statistically significant reduction in mean monthly migraine days and a statistically significant increase in the proportion of patients achieving a ≥50% reduction in monthly migraine days compared with placebo at 12 weeks. In the episodic migraine treatment group, the upper confidence interval for the change in monthly migraine days (-1.72 days) was less than the proposed minimum clinically important difference (MCID) of at least 2 days.
- 6.16 Health outcomes measured using the Migraine-Specific Quality of Life Questionnaire (MSQ), the Migraine Disability Assessment score (MIDAS), and the EQ-5D-5L in the ITT population and the episodic migraine subpopulation were provided in the submission. In the ITT population and the episodic migraine subpopulation, there was a statistically significant improvement from baseline in the MSQ total score and all domain scores in the galcanezumab treatment group compared with placebo. Similarly, there was a statistically significant reduction in perceived migraine-related disability (MIDAS total score) at Month 3 for patients in the galcanezumab treatment group compared with the placebo group. There was no statistically significant change from baseline in the EQ-5D for either treatment group.
- 6.17 Efficacy results for the CONQUER trial subgroup of patients with high frequency episodic migraine with 2 to 4 and 3 to 4 prior treatment failures are summarised in the table below.

**Table 7: Summary of results for the high frequency episodic migraine subgroups in the CONQUER trial, double blind treatment phase (12 weeks)**

	High frequency EM subgroup (2 to 4 prior treatments)			High frequency EM subgroup (3 to 4 prior treatments)		
	GAL N=102	PBO N=96	Difference (95% CI)	GAL N=48	PBO N=32	Difference (95% CI)
Change from baseline in number of monthly migraine headache days, LS mean (SE)	-3.09 (0.40)	-0.78 (0.40)	-2.31 (-3.26, -1.36)	-4.19 (0.58)	-1.76 (0.73)	-2.43 (-4.08, -0.79)
Change from baseline in number of monthly headache days, LS mean (SE)	-2.80 (0.41)	-0.25 (0.42)	-2.54 (-3.53, -1.56)	-4.04 (0.59)	-1.43 (0.75)	-2.61 (-4.28, -0.94)
≥50% responders, monthly migraine headache days, model estimated rate (SE)	36.7 (3.6)	17.5 (3.0)	19.2 (NR)	37.7 (5.3)	15.0 (4.8)	22.7 (NR)
≥30% responders, monthly migraine headache days (SE)	57.6 (NR)	32.8 (NR)	24.8 (NR)	57.3 (NR)	28.3 (NR)	29.0 (NR)
Change from baseline in MSQ Role Function-Restrictive Domain Score at Month 3, LS mean (SE)	20.62 (2.10)	9.47 (2.14)	11.15 (5.93, 16.37)	22.61 (3.06)	14.41 (3.83)	8.20 (-0.60, 16.99)

Source: Table 2.6.1, p61; Table 2.6.2, p62; Table 2.6.4, p63; Table 2.6.5, pp63-64; Table 2.7.3, pp72-74 of the resubmission; Section 3 economic model ('response' worksheet).

Abbreviations: CI, confidence interval; GAL, galcanezumab; LS, least squares; NR, not reported; █; PBO, placebo; SE, standard error.

- 6.18 Among patients with high frequency episodic migraine, treatment with galcanezumab was associated with a statistically significant reduction in monthly migraine headache days compared to placebo for patients with 2 to 4, or 3 to 4 prior treatments. The upper 95% confidence intervals for the 2 to 4 and 3 to 4 prior treatment groups were less than the proposed MCID of at least 2 days (-1.36 and -0.79), respectively.
- 6.19 Treatment with galcanezumab was also associated with a statistically significant reduction compared to placebo in monthly headache days, and a numerically higher proportion of patients achieving ≥50% reduction from baseline in monthly migraine days. Treatment with galcanezumab was associated with a statistically significant improvement in the MSQ Role Function-Restrictive Domain Score for patients with 2 to 4 prior treatments.

### **Comparative harms**

- 6.20 Adverse events reported in the overall trial population of the CONQUER trial are summarised in the table below.

**Table 8: Summary of key adverse events in the CONQUER trial (ITT population)**

	<b>Galcanezumab n with event/N (%)</b>	<b>Placebo n with event/N (%)</b>
<b>Overall summary of adverse events</b>		
Treatment emergent adverse events, n (%)	119/232 (51.29)	122/230 (53.04)
Treatment-related adverse events, n (%)	37/232 (15.95)	34/230 (14.78)
Serious adverse events, n (%)	2/232 (0.86)	2/230 (0.87)
Treatment-related serious adverse events, n (%)	0	0
Discontinuation related to adverse events, n (%)	1/232 (0.43)	0
<b>Summary of most frequently reported treatment emergent adverse events</b>		
Patients with ≥1 TEAE, n (%)	119 (51.29)	122 (53.04)
Nasopharyngitis	16 (6.90)	21 (9.13)
Influenza	11 (4.74)	7 (3.04)
Injection site erythema	8 (3.45)	6 (2.61)
Constipation	5 (2.16)	5 (2.17)
Injection site pain	5 (2.16)	13 (5.65)
Upper respiratory tract infection	5 (2.16)	5 (2.17)
Back pain	4 (1.72)	6 (2.61)
Nausea	4 (1.72)	5 (2.17)
Sinusitis	4 (1.72)	5 (2.17)
Migraine	1 (0.43)	5 (2.17)
Injection site reaction	0	6 (2.61)
Insomnia	0	5 (2.17)

Source: Table 2.6.8, p66; Table 2.6.9, p.67 of the resubmission.

Abbreviations: TEAE, treatment-emergent adverse event.

6.21 The overall incidence of adverse events was similar between treatment arms. There was a slightly greater incidence of treatment-related adverse events, and one discontinuation due to adverse events, in the galcanezumab treatment group.

6.22 The most common treatment-emergent adverse events (>2% of any group) were nasopharyngitis, influenza, injection site erythema, constipation, and injection site pain. Of the most common events, influenza and injection site erythema were reported more frequently in the galcanezumab group than the placebo group.

6.23 A summary of safety outcomes for the high frequency episodic migraine with 3 to 4 prior treatment failures subgroup is presented in the table below.

**Table 9: Summary of adverse events in the CONQUER high frequency episodic migraine with 3 to 4 prior treatments subgroup (double-blind treatment phase, 12 weeks)**

	<b>Galcanezumab n with event/N (%)</b>	<b>Placebo n with event/N (%)</b>
Treatment emergent adverse events, n (%)	27/48 (56.3)	16/32 (50.0)
Serious adverse events, n (%)	2/48 (4.2)	0/32 (0)
Discontinuation related to adverse events, n (%)	0/48 (0)	0/32 (0)
Deaths, n (%)	0/48 (0)	0/32 (0)

Source: Table 2.7.6, p75 of the resubmission.

6.24 The overall incidence of adverse events and serious adverse events was numerically higher in the galcanezumab arm compared to the placebo arm.

### **Benefits/harms**

- 6.25 On the basis of the direct evidence presented in the submission (12 weeks of double-blind treatment in CONQUER), for every 100 patients with chronic or episodic migraine and 2 to 4 prior treatment failures treated with galcanezumab 120 mg monthly in comparison to placebo:
- Approximately 24 more patients would have a  $\geq 50\%$  reduction in monthly migraine days.
  - Approximately 3 patients would have injection site pain.
- 6.26 On the basis of the direct evidence presented in the submission (12 weeks of double-blind treatment in CONQUER), for every 100 patients with episodic migraine and 2 to 4 prior treatments treated with galcanezumab 120 mg monthly in comparison to placebo:
- Approximately 25 more patients would have a  $\geq 50\%$  reduction in monthly migraine days.
- 6.27 On the basis of the direct evidence presented in the submission (12 weeks of double-blind treatment in CONQUER), for every 100 patients with high frequency episodic migraine and 3 to 4 prior treatment failures treated with galcanezumab 120 mg monthly in comparison to placebo:
- Approximately 23 more patients would have a  $\geq 50\%$  reduction in monthly migraine days.

### **Clinical claim**

- 6.28 The resubmission described galcanezumab as superior in terms of effectiveness, and similar in terms of safety compared with best supportive care, for the treatment of patients with high frequency episodic migraine (8 to 14 monthly migraine days) who have an inadequate response, intolerance or a contraindication to at least three prior prophylactic migraine medications.
- 6.29 The PBAC previously considered that the clinical claims of superior effectiveness and similar safety were supported for the broader population of patients with episodic migraine (patients with 4 to 14 monthly migraine days), but noted the benefit was modest and may not be realised in the population proposed for PBS listing.
- 6.30 The ESC considered the claim in the resubmission appeared to be reasonable, but the following issues should be considered:
- Whether the results of the post hoc analyses for the CONQUER subgroup of patients with 8 to 14 monthly migraine headache days and 3 to 4 prior treatment failures are reliable, given the small sample size and differences in patient characteristics between treatment arms. The ESC considered results should be interpreted with caution given the small sample size and given that the high frequency episodic migraine subgroup was not pre-specified in the CONQUER trial.

- The magnitude of the reduction in monthly migraine days in the CONQUER trial subgroup of patients with 8 to 14 monthly migraine headache days and 3 to 4 prior treatment failures was relatively small. The upper 95% confidence interval was less than the proposed minimal clinically important difference (MCID) of at least 2 days.
  - The duration of placebo-controlled trials was relatively short. There remains a lack of long-term comparative data to support the longer-term effectiveness and safety outcomes for galcanezumab.
- 6.31 The pre-PBAC response included clinician input that stated a reduction in monthly headache days of 2.43 was a substantial and clinically meaningful reduction. It was noted this was an average reduction and stated that some patients would have an excellent response (75% reduction), some would have a worthwhile response (50% reduction) and some patients would not respond to treatment (and cease the drug at the 3 month assessment).
- 6.32 The evaluation considered the applicability of the CONQUER trial results to the proposed PBS population was unclear, due to a lack of studies describing the Australian setting. The ESC agreed with the evaluation there was a lack of evidence whether disease severity, mean reductions in migraine headache days, and response rates observed in the trial will be similar in the proposed PBS population. However, the ESC considered that, overall, the CONQUER trial population was likely to be representative of Australian patients.
- 6.33 The PBAC considered that the claim of superior comparative effectiveness and similar safety was reasonable.

### ***Economic analysis***

- 6.34 The resubmission presented a stepped economic evaluation of galcanezumab compared to placebo (as a proxy for best supportive care), in patients with high frequency episodic migraine who have an inadequate response, intolerance or a contraindication to at least three prior prophylactic migraine medications.
- 6.35 A summary of the model structure and key inputs is presented in the table below. The model structure was unchanged from the November 2020 submission.

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Table 10: Summary of model structure and key inputs

Component	Resubmission
Type of analysis	Cost-effectiveness analysis and cost-utility analysis
Comparison	Galcanezumab versus placebo (as a proxy for best supportive care)
Outcomes	Migraine headache days; quality-adjusted life years (QALYs)
Time horizon	5 years in the model base case compared with 12 weeks in the CONQUER trial.
Methods used to generate results	Markov state transition model
Health states	On treatment/responder (after 12-week assessment) Discontinued (due to poor response) Discontinued (due to adverse events) Dead
Cycle length	One month (30 days)
Transition probabilities	Response rates from the CONQUER trial (high frequency episodic migraine with 3 to 4 prior treatment failures subgroup) Mean migraine headache days modelled from the observed migraine headache day distributions in the CONQUER using distributions derived from the EVOLVE 1 and 2 trials Discontinuation due to adverse events based on the CGAJ study Background mortality using annual age-specific mortality (ABS life tables)
Utilities	Utility -3L using an algorithm published by Gillard et al. (2012)
Costs	Galcanezumab drug costs based on the proposed effective DPMQ. No drug cost applied for placebo/best supportive care Acute medication use associated with each monthly migraine headache day predicted from CONQUER trial (ITT population, including both chronic and episodic migraine patients) using a binomial distribution. Unit costs based on PBS and OTC prices. Disease management costs (GP visits, specialist visits, nurse practitioner visits, emergency department visits, hospitalisations) by monthly migraine days based on the UK National Health and Wellness Survey (NHWS) included in the erenumab submission to NICE. Unit costs based on MBS, AR-DRG and Urgency Related Group items.
Software package	Microsoft Excel

Source: Section 3.1.2, p89; Section 3.2.2, pp98-100; Table 3.1.1, p88; Table 3.1.3, p90 of the resubmission.

Abbreviations: MSQ, Migraine-Specific Quality of Life Questionnaire; ITT, intention to treat

6.36 A summary of the key drivers of the economic model is presented in the table below.

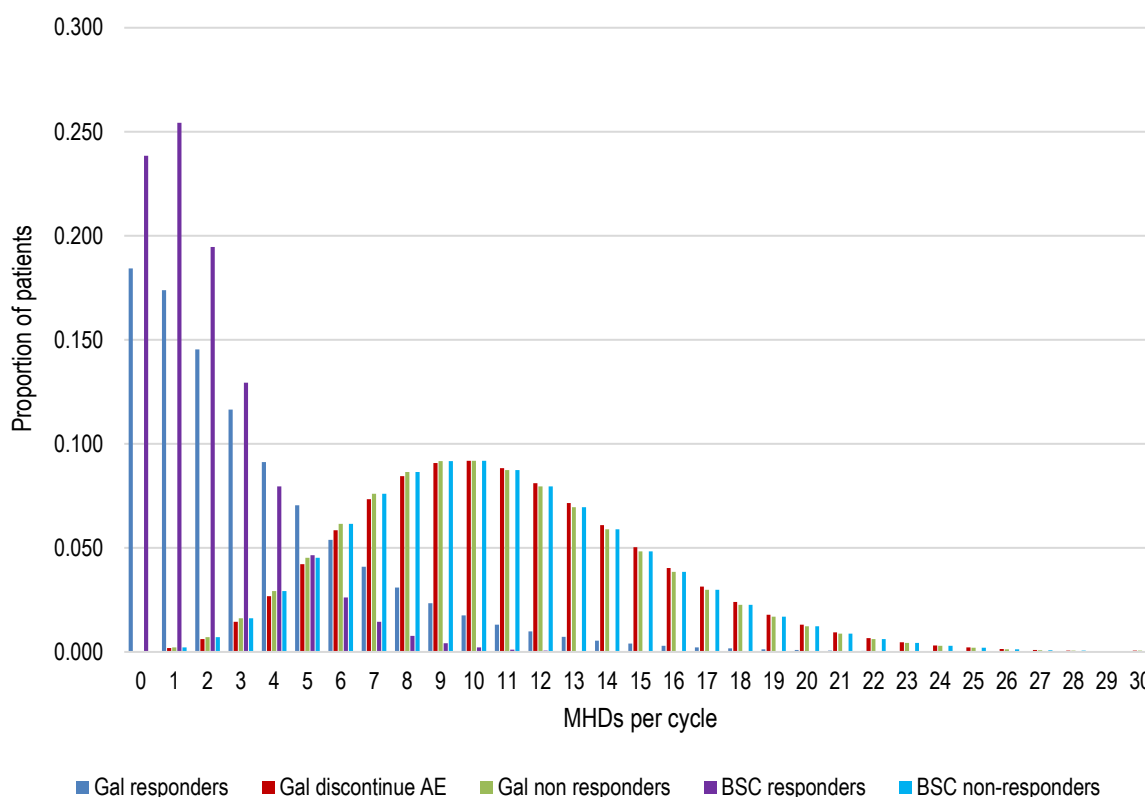
**Table 11: Key drivers of the model**

Description	Method/Value	Impact
Clinical evidence	The model applied a response-based stopping rule assessed at 3 months, where a response is defined as $\geq 50\%$ reduction in monthly migraine days from baseline, based on the proportion of patients who achieved this outcome in the relevant subgroup (37.7% in the galcanezumab treatment arm). There is a risk that a higher proportion of patients will continue treatment, who still achieve a significant clinical benefit from treatment with galcanezumab but without achieving the large decrease in migraine days associated with responders in the model (i.e., those with $< 50\%$ response rate). The inclusion of patients who do not achieve the large clinical benefit currently attributed to responders in the model is likely to markedly reduce the cost-effectiveness of galcanezumab, and this remains a substantial area of uncertainty.	High, favours galcanezumab
Monthly migraine day distributions	The distribution around the mean was based on a beta binomial distribution, with parameters derived from pooled data from the EVOLVE-1 and EVOLVE-2 trials (patients with episodic migraine with up to 2 prior treatment failures). The modelled distributions include people with monthly migraine headache days that would be outside of the restriction. At baseline in the economic model, 23.8% of the population were experiencing 0-7 monthly migraine headache days, and 19.7% were experiencing $\geq 15$ monthly migraine headache days. Given that costs and outcomes in the model are derived from these distributions, the results may not reflect the costs and outcomes for patients with high frequency episodic migraine with 8 to 14 monthly migraine days per month.	Uncertain
Extrapolation	The economic model assumed ongoing treatment for responders for the life of the model, with patients who met response criteria at Cycle 3 only subsequently able to discontinue due to adverse events or death. Mean monthly migraine headache day reductions reported for the high frequency episodic migraine with 3 to 4 prior treatment failures at 3 months were extrapolated to 5 years in the model. However, there is a lack of long-term clinical evidence to support this assumption.	High, favours galcanezumab
Utilities	The utility values were based on a subgroup analysis of patients with episodic or chronic migraine with 3 to 4 treatment failures from the CONQUER trial. It is unclear whether it was appropriate to include utilities based on populations who would be outside of the restriction (i.e., patients with chronic migraine). An improvement in utility associated with galcanezumab treatment independent of the number of monthly migraine days was applied in the model. This may duplicate the benefit of treatment in the model. Applying baseline utilities for each MHD to the 'on-treatment' health states significantly increased the ICER.	High, favours galcanezumab

Source: Compiled from Section 3 of the resubmission

- 6.37 Patients enter the model with an average of 10.86 migraine headache days per month (baseline). After 3 months of treatment, patients who achieve a  $\geq 50\%$  reduction in migraine days experience an average of 3.49 migraine headache days for galcanezumab-treated patients and 1.99 migraine headache days for best supportive care patients. Patients who discontinue treatment due to non-response after 3 months of treatment have a one month change in mean migraine headache days (-2.31 for galcanezumab; -0.22 for best supportive care) before returning to baseline. Patients who discontinue treatment due to adverse events over the duration of the model return to baseline migraine headache days over 13 months.
- 6.38 Modelled distributions were based on the placebo group in the EVOLVE studies. The average modelled distributions of monthly migraine headache days used in the economic model are summarised in Figure 1.

Figure 1: Mean predicted distributions of migraine headache days per cycle by health state (post response assessment)



Source: Constructed during the evaluation using the Section 3 economic model.

Abbreviations: AE, adverse event; BSC, best supportive care; MHD, migraine headache day.

Note that the results presented in Figure 1 are derived during the evaluation by the PBAC specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.39 The modelled mean distributions over a 5-year time horizon highlight the low monthly migraine headache days associated with patients in the responder health states, most of whom achieved 0, 1, or 2 migraine headache days per cycle. Patients who discontinued galcanezumab due to an adverse event, and non-responders in both arms accrued more monthly migraine headache days in each cycle.

6.40 The utilities applied in the model are summarised in the table below.

**Table 12: Average utility estimates in the economic model**

Health state/cycle	Galcanezumab	BSC	Source
<b>Prior to response assessment</b>			
On treatment			
- Cycle 1	0.5849	0.5849	Based on distribution of headache days associated with baseline migraine headache days per month (10.86); multiplied by corresponding baseline utilities in cycle 1; and by response utilities (which vary by treatment arm) in cycles 2 and 3
- Cycle 2-3	0.6763	0.6190	
Off treatment (adverse event)			
- Cycles 2-3	0.5849	0.5849	Based on distribution of headache days associated with baseline migraine headache days per month (10.86); multiplied by baseline utilities
<b>After response assessment</b>			
On treatment			
- Cycles 4+	0.7596	0.7192	Based on distribution of headache days associated with mean migraine headache days per month for responders (3.49 for galcanezumab; 1.99 for BSC); multiplied by corresponding response utilities (which vary by treatment arm)
Off treatment (non-response)			
- Cycle 4	0.6201	0.5883	For cycle 4, based on distribution of headache days associated with mean migraine headache days per month for non-responders (8.55 for galcanezumab; 10.64 for BSC). It is assumed that treatment washout period is one cycle, therefore from cycle 5 distribution of headache days is based on baseline migraine headache days (10.86). Migraine days are multiplied by corresponding baseline utilities
- Cycle 5+	0.5849	0.5849	
Off treatment (adverse event)			
- Cycles 4+	0.5822 - 0.6510	-	Varies by cycle according to assumed waning of treatment effect over 13 cycles following discontinuation. Mean migraine headache days per month varies from 6.52 to 11.04.

Source: [REDACTED]

Abbreviations: BSC, best supportive care.

Note that the results presented in Table 12 are derived during the evaluation by the PBAC specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

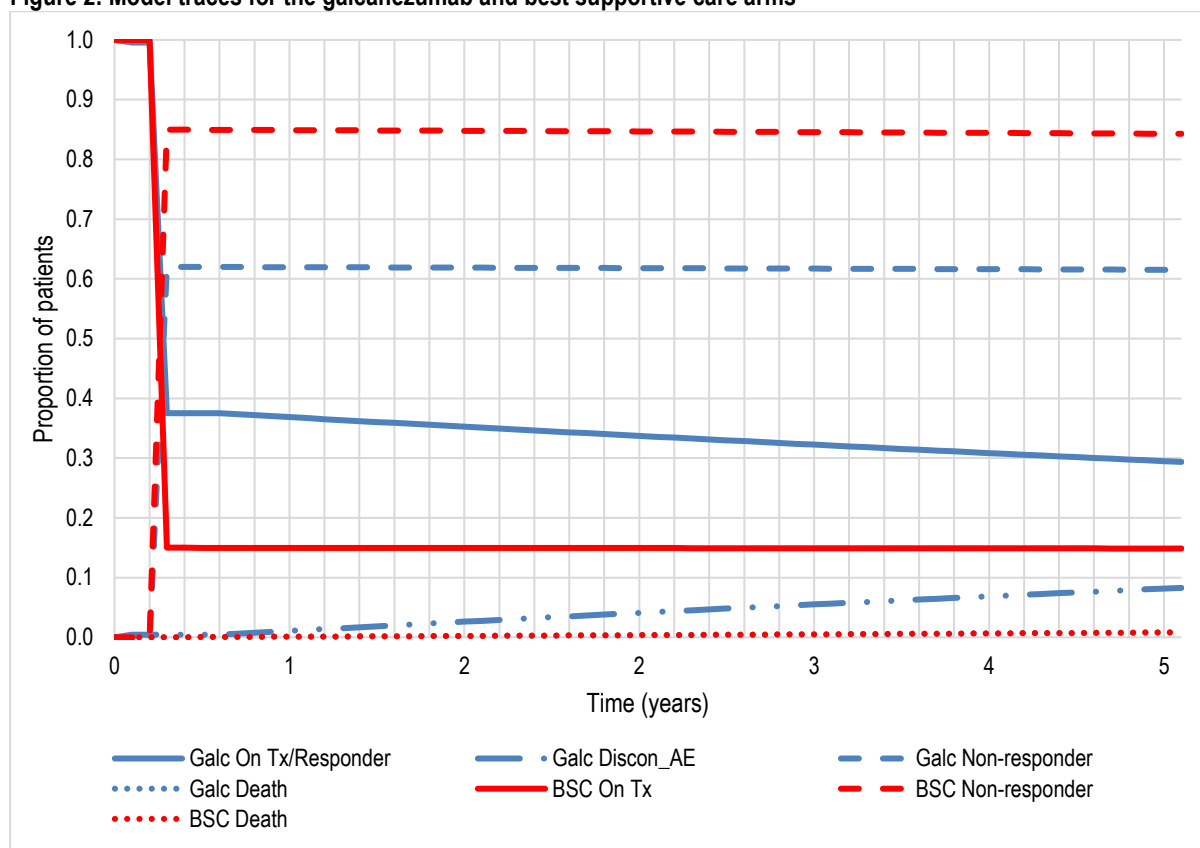
- 6.41 While EQ-5D data were collected in the CONQUER trial, the resubmission argued that it did not accurately capture the impact of disease on patient’s quality of life, as it was only administered at baseline and at the end of the trial period, and patients experiencing a migraine may be less likely to attend clinical appointments. The resubmission argued that, in contrast, the Migraine Specific Quality of Life Questionnaire (MSQ) was administered monthly throughout the randomised and post-treatment phases on the trial and has a four-week recall period, which may mean it was able to capture more granular changes in health-related quality of life. The EQ-5D-5L scores collected during the CONQUER trial show no statistically significant difference between treatment arms, while mapped MSQ utility values used in the economic model favour treatment with galcanezumab.
- 6.42 There was a large utility benefit associated with being on galcanezumab treatment, both compared with baseline/off-treatment values, and compared with those on-treatment in the best supportive care arm. A technical document provided as part of the resubmission stated that the MSQ-derived utilities suggest higher utility values for patients receiving galcanezumab than for patients receiving placebo for the same number of migraine headache days, and that this may indicate that galcanezumab may have a benefit beyond reducing the number of monthly migraine headache days.

- 6.43 The ESC previously considered that it was unclear whether the application of a utility benefit for being on treatment with galcanezumab compared with best supportive care was appropriate, and likely double counts the benefit of treatment in the model (Paragraph 6.51, galcanezumab PSD, November 2020 PBAC meeting).
- 6.44 The resubmission presented the results of a correlation analysis to support the inclusion of a utility benefit for patients on treatment with galcanezumab in the model. In the episodic migraine population, correlations with the frequency of monthly migraine headache days at Month 3 were low or negligible for all outcomes apart from MSQ Total and MSQ-Role Function Restrictive (moderate), and symptom-free headache free days (high). A moderate correlation was found at Month 6 between migraine headache day and MSQ-Role Function Restrictive and a high correlation between migraine headache day and symptom-free headache free days.
- 6.45 The resubmission argued that based on the correlation analysis, symptoms associated with the intensity and severity of pain of a migraine attack, disability caused by migraine attacks, or impact of health-related quality of life between attacks are unlikely to be explained by a change in migraine headache day frequency alone. The Pre-Sub-Committee Response (PSCR) reiterated the arguments presented in the resubmission that analyses provided in the resubmission show that migraine headache days alone are poorly correlated with other specific measures of health status used to capture the impact of migraine on QoL. The PSCR stated it is therefore reasonable that utility values applied in the model are separated for patients on galcanezumab treatment and BSC in the 'On-treatment' health state.
- 6.46 The ESC considered it remained uncertain whether treatment with galcanezumab would have a QoL benefit in addition to the direct modelled benefit of a reduction in MHD. The ESC acknowledged migraine has a significant impact on quality of life, in addition to the number of migraine headache days, but considered the evidence provided (which was based on small patient numbers with limited follow up) did not support galcanezumab providing an additional QoL benefit. The ESC noted the extent of the 'on treatment' utility benefit (as outlined in Table 12), and that the model was highly sensitive to this assumption with the ICER increasing from \$25,000 to < \$35,000/ QALY to \$55,000 to < \$75,000/ QALY assuming no 'on treatment' utility benefit. The ESC considered that in the absence of reliable evidence to support an 'on treatment' utility benefit for galcanezumab, that it should be excluded from the base case analysis.
- 6.47 The clinician input provided with the pre-PBAC response stated that, in addition to a reduction in the number of migraine headache days, treatment with galcanezumab can reduce the severity of migraine with episodes shorter and more easily managed. It stated non-headache symptoms such as nausea, postdromal lethargy and malaise are also reduced. The statement also indicated CGRP antibodies can be highly effective in reducing interictal burden (whereby patients avoid everyday activities if they have frequent migraine episodes). The pre-PBAC response stated measures such as severity and aspects of QoL such as interictal burden, disability and functional impairment, that

aren't captured within a measure for a MHD, should be included in the economic evaluation in order to capture the full impact on QoL. The pre-PBAC response stated that using treatment specific utilities, as opposed to only a utility value assigned to MHD reduction, is the way that these additional aspects can be captured within the economic evaluation.

6.48 The model trace is summarised in the figure below.

Figure 2: Model traces for the galcanezumab and best supportive care arms



Source: [Redacted]

Abbreviations: AE, adverse event; BSC, best supportive care; Discon, discontinuation; Galc, galcanezumab; Tx, treatment.

Note that the results presented in Figure 2 are derived during the evaluation by the PBAC specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.49 The Markov trace indicates that treatment with galcanezumab was associated with more time spent in the on-treatment responder health state, and less time in the discontinuation health states (either due to adverse events or non-response), compared with best supportive care.

6.50 At the end of Year 5, approximately 29% of patients remain on treatment with galcanezumab, continuing to achieve a response rate of  $\geq 50\%$  (November 2020 submission: 32%). It is unclear whether these proportions of responders and non-responders will be replicated in practice. Given the lack of available treatments for

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patients with episodic migraine who have inadequate response, intolerance or a contraindication to  $\geq 3$  prior treatments, and the difficulty in assessing response in clinical practice, patients with smaller reductions in monthly migraine headache days may remain on treatment. It is also unclear whether the treatment effect in responders will be maintained indefinitely.

6.51 The results of the stepped economic analysis, including additional steps calculated during the evaluation, are provided in the table below.

**Table 13: Results of the stepped economic evaluation**

	Galcanezumab	BSC	Increment
<b>Step 1a: Trial-based analysis, difference in migraine days over 12-weeks, drug costs only</b>			
Costs	\$	\$	\$
Mean reduction in migraine days	-4.2	-1.8	-2.4
Incremental cost per migraine headache day avoided			\$
<b>Step 1b: Modelled analysis, difference in migraine days in cycle 4 (after 3-month assessment period), drug costs over 3 cycles (approximately 12 weeks)</b>			
Costs	\$	\$	\$
Mean reduction in migraine days	-4.2	-1.5	-3.2
Incremental cost per migraine headache day avoided			\$
<b>Step 2a: Difference in migraine days, drug costs over 12 months</b>			
Costs	\$	\$	\$
Total migraine days	112.0	127.6	-15.6
Incremental cost per migraine headache day avoided			\$
<b>Step 2b: Difference in migraine days, drug costs, acute treatment and migraine management costs over 12 months</b>			
Costs	\$	\$	\$
Total migraine days	112.0	127.6	-15.6
Incremental cost per migraine headache day avoided			\$
<b>Step 3: Utilities applied to health states to generate QALYs; costs over 12 months</b>			
Costs	\$	\$	\$
QALYs	0.694	0.647	0.048
Incremental cost per QALY gained			\$ <sup>1</sup>
<b>Step 4: QALYs and costs over 5-year time horizon</b>			
Costs	\$	\$	\$
QALYs	2.934	2.752	0.183
Incremental cost per QALY gained			\$ <sup>2</sup>

Source: Table 3.8.2, p142 of the resubmission; additional analyses calculated during the evaluation using the Section 3 economic model. Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.

The redacted values correspond to the following ranges:

<sup>1</sup> \$45,000 to < \$55,000

<sup>2</sup> \$25,000 to < \$35,000

6.52 Based on the results of the economic model, treatment with galcanezumab was associated with an incremental cost per migraine day averted over a 12-month period of \$ (November 2020 submission: \$), and a cost per QALY gained over 5 years of \$25,000 to < \$35,000 (November 2020 submission: \$35,000 to < \$45,000), compared to best supportive care (placebo). The difference compared to the November 2020 submission was primarily due to a reduction in the proposed galcanezumab price.

6.53 The evaluation noted the following issues:

- The economic model assumed that only patients who achieved a  $\geq 50\%$  reduction in monthly migraine days at 3 months would continue treatment with galcanezumab. In practice it is likely that some patients who do not achieve the required 50% response will continue treatment if they have achieved a clinically meaningful reduction in monthly migraine days. The subjective nature of the proposed continuation criteria and a current lack of PBS-listed treatment alternatives for this population may also contribute to a higher continuation rate in clinical practice.
- The economic model assumed ongoing treatment for responders for the life of the model, with patients only discontinuing due to adverse events or death after the initial response assessment. There is a lack of long-term clinical evidence to support the durability of treatment effect for patients achieving a  $\geq 50\%$  response at 3 months. The PSCR stated extensive long-term evidence was provided in the resubmission and therefore it is reasonable to assume that for the patients that remain on galcanezumab treatment in the model, the treatment effect of galcanezumab does not wane over time of the 5-year time horizon of the model. The ESC noted the evidence from the open-label extension studies was limited to a maximum of 12 months and considered the appropriateness of assuming no waning of effect over 5 years remained uncertain.
- The modelled distributions included a large proportion of patients who would either not be eligible under the proposed restriction or would fit the definition for chronic migraine. At baseline in the economic model, 23.8% of the population were experiencing 0-7 monthly migraine headache days, and 19.7% were experiencing  $\geq 15$  monthly migraine headache days. As costs and outcomes in the model were derived from these distributions, the modelled results may not reflect the costs and outcomes for patients with high frequency episodic migraine. The PSCR argued that the impact of the distributions is limited during the initial three months of the model, given that the same distribution is applied to the galcanezumab and BSC arms. The ESC considered that the overall impact of the distribution on the results is uncertain; however, noted it may not be substantial given that patients with  $\geq 15$  monthly migraine headache days (19.7%) were somewhat balanced by patients experiencing 0-7 monthly migraine headache days (23.8%).
- It remains uncertain whether the application of a utility benefit for being on treatment with galcanezumab compared with best supportive care is appropriate. The ESC agreed with the evaluation that this remained uncertain (as discussed in paragraph 6.46).
- The results for the subgroup of patients with high frequency episodic migraine with 3 to 4 prior treatment failures were based on the results of a post hoc analysis which was considered to be at high risk of bias. Additionally, the results were based on small patient numbers.

6.54 Key sensitivity analyses presented in the submission and conducted during the evaluation are summarised in the table below.

Table 14: Results of key sensitivity analyses

	Incremental cost (\$)	Incremental QALYs	ICER (\$)
<b>Base case</b>		<b>0.183</b>	<sup>2</sup>
<b>Discount rate (base case % for costs and benefits)</b>			
% for costs and benefits		0.199	<sup>2</sup>
% for costs and benefits		0.187	<sup>2</sup>
<b>Time horizon (base case 5 years)</b>			
1 year		0.048	<sup>3</sup>
3 years		0.124	<sup>2</sup>
10 years		0.277	<sup>2</sup>
<b>Proportion of responders (base case response based on ≥50% reduction for the CONQUER trial high frequency episodic migraine 3 to 4 prior treatments)</b>			
Response based on ≥50% reduction in mean MHD for high frequency episodic migraine 2 to 4 prior treatments subgroup		0.170	<sup>2</sup>
Response based on ≥30% reduction in mean MHD for high frequency episodic migraine 3 to 4 prior treatments subgroup		0.240	<sup>4</sup>
Galcanezumab ≥50% responders increased from 37.7% to 47.7%		0.251	<sup>2</sup>
Galcanezumab ≥50% responders reduced from 37.7% to 27.7%		0.115	<sup>4</sup>
<b>Duration of treatment effect (base case for duration of model)</b>			
BSC loss of efficacy after 1 year		0.240	<sup>5</sup>
10% reduction in mean MHD reduction per year for responders		0.172	<sup>4</sup>
20% reduction in mean MHD reduction per year for responders		0.162	<sup>4</sup>
<b>Utility values (base case different utilities per migraine headache day applied to baseline/off treatment, galcanezumab on treatment and BSC on treatment health states)</b>			
Pooled on-treatment utilities		0.118	<sup>3</sup>
Baseline (off-treatment) utilities applied to all health states		0.082	<sup>6</sup>

Source: Table 3.9.2, p146 of the resubmission; additional analyses conducted using the Section 3 economic model.

Abbreviations: BSC, best supportive care; CI, confidence limit; ICER, incremental cost effectiveness ratio; MHD, migraine headache days; QALY, quality adjusted life year.

<sup>1</sup> Based on calculation in parameters worksheet of model spreadsheet, corrected to 95% rather than 90% confidence interval

The redacted values correspond to the following ranges:

<sup>2</sup> \$25,000 to < \$35,000

<sup>3</sup> \$45,000 to < \$55,000

<sup>4</sup> \$35,000 to < \$45,000

<sup>5</sup> \$15,000 to < \$25,000

<sup>6</sup> \$55,000 to < \$75,000

6.55 The results of sensitivity analyses indicate that the model was most sensitive to changes in the assumed utility values, the mean monthly migraine headache day reductions achieved by responders, whether the treatment effect was maintained, and the model time horizon. Due to the structure of the economic model, it was difficult to assess different scenarios exploring alternative distributions of patients across monthly migraine headache days, or the impact of patients with <50% response continuing treatment.

### **Drug cost/patient/year**

6.56 The drug cost per patients for galcanezumab is presented in the table below.

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Table 15: Drug cost per patient for galcanezumab

	Economic model	Financial estimates
Dose	240 mg loading dose followed by 120 mg monthly	240 mg loading dose followed by 120 mg monthly
Drug cost per dose (effective DPMQ)	\$	\$
<b>Initial year</b>		
Adherence	100%	100%
Cost/patient/year (excluding response assessment)	\$ <sup>a</sup>	\$ <sup>b</sup>
Response rate	37.7%	40%
Cost including response assessment	\$ <sup>c</sup>	\$ <sup>d</sup>
<b>Subsequent years</b>		
Adherence	100%	100%
Scripts per year	12.175	12
Cost/patient/year <sup>e</sup>	\$	\$

Source: Compiled using the Section 3 economic model and Section 4 financial impacts workbook.

<sup>a</sup> Calculated based on 13.175 doses per year (inclusive of initial loading dose) x DPMQ of \$|.

<sup>b</sup> Calculated based on 13 doses per year (inclusive of initial loading dose) x DPMQ of \$|.

<sup>c</sup> Calculated based on initial 4 administrations including loading dose x DPMQ of \$|, plus 37.7% responders x 9.175 subsequent administrations x DPMQ of \$|.

<sup>d</sup> Calculated based on initial 4 administrations including loading dose x DPMQ of \$|, plus 40% responders x 9 subsequent administrations x DPMQ of \$|.

<sup>e</sup> In the economic model, 0.43% discontinued treatment each cycle (approximately 5.4% per year). In the financial estimates, 5% of patients were assumed to discontinue treatment each year.

Abbreviations: DPMQ, dispensed price for maximum quantity; |.

6.57 The average cost per patient of galcanezumab in the initial year of treatment was \$| in the economic model, \$| in the financial estimates. The average cost per patient of galcanezumab in subsequent years was \$| in the economic model and \$| in the financial estimates. The difference between the economic model and financial estimates was due to differences in the assumed response rates and numbers of scripts.

**Estimated PBS usage & financial implications**

6.58 This resubmission was not considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impacts associated with the requested listing.

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Table 16: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Migraine prevalence	22.8%; Based on the estimated Australian 2017 prevalence reported in The Global Burden of Disease study, presented as a sensitivity analysis in the November 2020 galcanezumab commentary.	Increased from the November 2020 submission prevalence estimate of 14.6% based on the weighted average of patients with migraine, aged $\geq 15$ years reported by Stark et al. (2007). The all-age prevalence of migraine reported by the GBD study has been updated, with reported prevalence estimates of 14.75%, 14.77% and 14.86% for 2017, 2018 and 2019, respectively. These estimates are similar to the Stark et al. estimate included in the November 2020 submission, and more closely aligned with the estimated global migraine prevalence of migraine reported by the GBD study (2019 global all-age prevalence of 15.16%) The ESC considered a migraine prevalence of 14.64% based on the Stark study was reasonable and consistent with previous considerations of migraine treatments.
Proportion of migraine that is episodic migraine	92.39%; Proportion of migraine that is chronic migraine assumed to be 7.61% based on the proportion reported in Deloitte Access Economics Whitepaper on Migraine in Australia (2018), which was based on chronic migraine estimates reported for the AMPP study (Buse et al., 2012), applied to Australia's demographic structure. The complement proportion was assumed to have episodic migraine (i.e., $100\% - 7.61\% = 92.39\%$ ).	The November 2020 episodic and chronic migraine submissions assumed that 10% of patients had chronic migraine and 90% had episodic migraine. The PSCR stated that to address the concern around double counting, it would be reasonable to assume 90% of patients had episodic migraine, consistent with the previously approved chronic migraine estimates. The PBAC agreed with the PSCR amendment.
Proportion of episodic migraine that is high frequency episodic migraine	19.5%; Based on the results of an online survey of GPs (n=87) and neurologists (n=30) conducted by the sponsor. Based on the average of 13% reported by general practitioners and 26% reported by neurologists.	There were large differences in the survey results for GPs and neurologists. The evaluation considered it may not be reasonable to average the results of general practitioners and neurologists, given that GPs are likely to treat all patients whereas neurologists are likely to see patients with more severe disease.
Proportion currently taking an oral preventative	74.5%; Based on the results of an online survey of GPs (n=87) and Neurologists (n=30) conducted by the sponsor. Based on the average of 67% reported by general practitioners and 82% reported by neurologists.	The proposed restriction does not require patients to be currently using an oral migraine preventative. The evaluation noted that some patients who have failed $\geq 3$ prior migraine preventative therapies may have ceased all prophylactic treatments, due to a lack of efficacious therapies.
Proportion currently taking $\geq 3$ oral preventatives	10%; Based on the results of an online survey of GPs (n=87) and neurologists (n=30) conducted by the sponsor. Neurologists reported 10% of patients and GPs reported 5% of patients were currently taking $\geq 3$ oral preventatives.	The resubmission assumed that only patients currently taking $\geq 3$ oral migraine treatments would be treated. The evaluation noted that as current treatment with $\geq 3$ prophylactic treatment is not a requirement under the proposed restriction, this step should not have been included.
Proportion currently taking $\geq 3$ oral preventatives and are intolerant, contraindicated, or have failed $\geq 3$ preventative treatments	48%; Based on the results of an online survey of GPs (n=87) and Neurologists (n=30) conducted by the sponsor. Among patients taking $\geq 3$ oral preventive treatments, an average of 48% are treatment resistant (not achieving adequate response, intolerance or contraindicated to $\geq 3$ prophylactic migraine medication).	The proportion of patients who are treatment resistant (not achieving adequate response, intolerance or contraindicated to $\geq 3$ prophylactic migraine medication) was based on patients currently taking $\geq 3$ oral preventatives which the evaluation considered was not consistent with the proposed restriction.

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Parameter	Value applied and source	Comment
Continuing patients (patients with response)	40%; Based on the proportion included in the November 2020 galcanezumab chronic migraine minor resubmission.	This was higher than the response rate reported for the high frequency subgroup with ≥3 prior treatments in the CONQUER trial used in the economic model (37.7%). However, some patients who achieve less than a 50% reduction in migraine headache days may continue treatment (i.e., outside of the proposed restriction) if a clinically meaningful reduction in migraine headache days is achieved.
Continuation rate in subsequent years	95%; Based on the proportion included in the November 2020 galcanezumab chronic migraine minor resubmission.	Continuation rates among patients with episodic migraine may be lower than estimated.
Grandfathered patients	The resubmission estimated that approximately <500 patients from the sponsor's access program would be treatment with galcanezumab under the proposed listing. Based on the assumption that 40% of patients achieve a ≥50% response and continue treatment at 12 weeks, and 95% of responders continue in subsequent years.	These patients would already be accounted for in the resubmission's estimates of eligible patients.
Galcanezumab price	\$█ (AEMP)/\$█ (DPMQ); Proposed effective price for galcanezumab.	-
MBS costs	\$79.75; Neurologist visits (MBS item 116), first visit, after 3 treatment cycles, then ongoing follow-up every 6 treatment cycles; 2 visits in first 3 months, one additional visit in Year 1 for continuing patients, then 2.03 visits/year after the first year.	The estimates are likely to be overestimated, given that a large proportion of patients would be managed by their GP after an initial consultation with a neurologist.

Source: Table 4.1.2, pp149-150; Table 4.1.3, pp150-151 of the resubmission.

Abbreviations: AEMP, approved ex-manufacturer price; █ American Migraine Prevalence and Prevention; DPMQ, dispensed price for maximum quantity; GBD, Global Burden of Disease; GP, general practitioner.

6.59 The estimated utilisation and financial impact of listing galcanezumab for high frequency episodic migraine is presented in the table below.

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Table 17: Estimated utilisation and financial impact of listing galcanezumab for high frequency episodic migraine

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Australian population (18 to 90 years of age)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Migraine prevalence (22.8%)	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>20</sup>
Patients with EM (92.4%)	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
Proportion of EM that is high frequency (19.5%)	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>21</sup>
Patients currently using an oral preventative (74.5%)	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
Patients currently on ≥3 oral preventatives (10%)	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>
On ≥3 preventatives and intolerant, contraindicated, or have failed ≥3 preventative treatments (48.0%)	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>
Uptake rates	█ <sup>9%</sup>	█ <sup>9%</sup>	█ <sup>9%</sup>	█ <sup>9%</sup>	█ <sup>9%</sup>	█ <sup>9%</sup>
Number of patients initiating treatment (cumulative)	█ <sup>7</sup>	█ <sup>13</sup>	█ <sup>13</sup>	█ <sup>10</sup>	█ <sup>10</sup>	█ <sup>10</sup>
Number of new patients per year (estimated by subtracting patients from previous years)	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>
Patients continuing treatment (responders; 40%)	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>8</sup>
Continuing patients (subsequent years; 95%)	█ <sup>9</sup>	█ <sup>8</sup>	█ <sup>8</sup>	█ <sup>7</sup>	█ <sup>7</sup>	█ <sup>7</sup>
Grandfathered patients	█ <sup>9</sup>	█ <sup>9</sup>	█ <sup>9</sup>	█ <sup>9</sup>	█ <sup>9</sup>	█ <sup>9</sup>
Scripts dispensed (initial 3 months)	█ <sup>10</sup>	█ <sup>10</sup>	█ <sup>13</sup>	█ <sup>13</sup>	█ <sup>13</sup>	█ <sup>7</sup>
Scripts dispensed (continuing, including grandfathered patients)	█ <sup>10</sup>	█ <sup>14</sup>	█ <sup>16</sup>	█ <sup>17</sup>	█ <sup>19</sup>	█ <sup>22</sup>
<b>Net cost to PBS/RPBS (less copayments)<sup>a</sup> (\$)</b>	█ <sup>11</sup>	█ <sup>15</sup>	█ <sup>15</sup>	█ <sup>18</sup>	█ <sup>18</sup>	█ <sup>18</sup>
Net cost to MBS (\$)	█ <sup>12</sup>	█ <sup>12</sup>	█ <sup>12</sup>	█ <sup>12</sup>	█ <sup>12</sup>	█ <sup>12</sup>
<b>Net cost to Government (\$)</b>	█ <sup>11</sup>	█ <sup>15</sup>	█ <sup>15</sup>	█ <sup>18</sup>	█ <sup>18</sup>	█ <sup>18</sup>

Source: Table 4.2.2, p154; Table 4.2.3, p156; Table 4.2.4, p157; Table 4.2.5, p158; Table 4.2.6, p159; Table 4.2.7, pp159-160; Table 4.2.9, p161; Table 4.2.10, p161; Table 4.5.4, p164 of the resubmission.

Abbreviations: EM, episodic migraine; MBS, Medicare Benefits Scheme.

<sup>a</sup> Based on proposed DPMQ of \$█, PBS copayment of \$28.49, and RPBS copayment of \$5.19.

The redacted values correspond to the following ranges:

<sup>1</sup> > 10,000,000

<sup>2</sup> 4,000,000 to < 5,000,000

<sup>3</sup> 800,000 to < 900,000

<sup>4</sup> 600,000 to < 700,000

<sup>5</sup> 60,000 to < 70,000

<sup>6</sup> 30,000 to < 40,000

<sup>7</sup> 5,000 to < 10,000

<sup>8</sup> 500 to < 5,000

<sup>9</sup> < 500

<sup>10</sup> 20,000 to < 30,000

<sup>11</sup> \$10 million to < \$20 million

<sup>12</sup> \$0 to < \$10 million

<sup>13</sup> 10,000 to < 20,000

<sup>14</sup> 50,000 to < 60,000

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<sup>15</sup> \$20 million to < \$30 million

<sup>16</sup> 70,000 to < 80,000

<sup>17</sup> 80,000 to < 90,000

<sup>18</sup> \$30 million to < \$40 million

<sup>19</sup> 90,000 to < 100,000

<sup>20</sup> 5,000,000 to < 6,000,000

<sup>21</sup> 900,000 to < 1,000,000

<sup>22</sup> 100,000 to < 200,000

- 6.60 The estimated net cost of listing galcanezumab on the PBS/RPBS for high frequency episodic migraine was \$10 million to < \$20 million in Year 1, increasing to \$30 million to < \$40 million in Year 6 of listing, an estimated net cost of \$100 million to < \$200 million over the first six years of listing.
- 6.61 The resubmission estimated a total net cost to the health budget of \$10 million to < \$20 million in Year 1, increasing to \$30 million to < \$40 million in Year 6, an estimated net cost of \$100 million to < \$200 million over the first six years of listing. The November 2020 submission (based on a broader requested patient population) estimated a net cost to the health budget of \$400 million to < \$500 million over the first six years of listing.
- 6.62 Some patients who achieve less than a 50% reduction in migraine headache days may continue treatment (i.e., outside of the proposed restriction) if a clinically meaningful reduction in migraine headache days has been achieved.
- 6.63 The resubmission inappropriately added the grandfathered patients to the epidemiological estimates. The evaluation considered these patients would already be captured in the resubmission's estimates of prevalent patients. The PSCR stated grandfathered patients within the financial estimates represent the number of patients that are continuing treatment only and are not added to the initiation eligible patient pool. The PSCR stated the consideration of grandfathered continuation patients to the financial estimates correctly determines the net financial impact of all patients continuing treatment with galcanezumab. The ESC agreed with the evaluation that as advised in the ['User Manual and Cost Model Workbook'](#) version 1.4 page 21, it would be expected that grandfathered patients, including those continuing on treatment, would be already captured in estimates for prevalent patients. The PBAC advised that separate consideration of grandfathered patients was not appropriate.
- 6.64 The resubmission estimated a migraine prevalence of 22.8%, based on the prevalence reported in the Global Burden of Disease study, which has subsequently been updated. Updated prevalence estimates for the Global Burden of Disease Study now suggest a lower Australian migraine prevalence (14.86%; 2019 all-ages estimate), which is more consistent with the 2019 GBD global estimate of 15.16% and the Stark et al. (2007) estimate of 14.5% included in the 2020 galcanezumab episodic migraine submission. The PBAC agreed with the ESC that a migraine prevalence as reported in the Stark publication would be appropriate, consistent with previous considerations

of migraine. The PBAC also considered it was appropriate to assume 90% of patients with migraine had episodic migraine for consistency with previous considerations.

- 6.65 The ESC considered the resubmission's financial estimates were highly uncertain for the reasons outlined in Table 16.
- 6.66 The PBAC considered that with some amendments (as outlined in paragraph 6.64), the estimated number of patients with high frequency episodic migraine was reasonable. The PBAC considered that only a small proportion of patients with high frequency episodic migraine would be eligible for treatment with galcanezumab and overall, the approach to estimating the proportion of patients that would be eligible for treatment in the resubmission was reasonable.

### ***Quality Use of Medicines***

- 6.67 The resubmission listed the following planned activities to support the quality use of medicines: routine pharmacovigilance activities, online medical education modules, scientific meetings, and the development of additional educational activities for clinicians.

### ***Financial Management – Risk Sharing Arrangements***

- 6.68 The sponsor proposed a risk-sharing arrangement (RSA) consisting of an overall CGRP inhibitor cap for patients with treatment-resistant migraine (i.e., patients with high frequency episodic migraine and chronic migraine). The resubmission stated that a separate high-frequency episodic migraine cap (in addition to the current chronic migraine RSA cap) could also be considered.
- 6.69 The high frequency episodic migraine Tier 1 cap was derived based on the submission's 'maximum eligible population' scenario, with galcanezumab uptake rates of |%, |%, |%, |% and |% in Years 2 to 6 of the RSA, respectively. The proposed Tier 2 cap was also based on the 'maximum eligible population' scenario uptake rates but assumed that a higher proportion of patients continue treatment with galcanezumab at 3 months (|%; based on the proportion of patients achieving a ≥30% reduction in monthly migraine headache days). The Tier 1 and 2 caps were obtained by multiplying the estimated script volumes by the proposed galcanezumab AEMP of \$|, with no adjustment for patient copayments or MBS costs. For both Tier 1 and Tier 2, |% of responding patients were assumed to continue treatment in each subsequent year. The ESC considered that any expenditure cap should be based on the financial estimates as presented above, rather than a 'maximum eligible population'. The pre-PBAC response maintained the expenditure caps should be based on the 'maximum eligible population' but stated it was willing to negotiate with the Department should the PBAC recommended the RSA population should sit somewhere between the base and high cases. The PBAC agreed with the ESC that is appropriate for expenditure caps to be based on the financial estimates.

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6.70 Components of the current chronic migraine CGRP cap, the proposed high frequency episodic migraine cap, and the proposed combined treatment-resistant migraine cap, are summarised in the table below.

Table 18: Proposed risk-sharing arrangement parameters

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Current chronic migraine CGRP inhibitor cap parameters</b>						
Specified months	Jun 21 - May 22	Jun 22 - May 23	Jun 23 - May 24	Jun 24 - May 25	Jun 25 - May 26	Jun 26 - May 27
Script volumes totals	1	3	9	9	9	9
Tier 1 █ % rebate (\$)	2	2	4	4	4	4
Tier 2 █ % rebate (\$)	2	4	7	7	7	7
<b>Proposed high frequency episodic migraine cap parameters</b>						
Months specified	Aug 21 - Jul 22	Aug 22 - Jul 23	Aug 23 - Jul 24	Aug 24 - Jul 25	Aug 25 - Jul 26	Aug 26 - Jul 27
Script volumes totals <sup>a</sup>	-	5	10	9	9	9
Tier 1 █ % rebate (\$)	-	2	4	7	7	7
Script volumes totals <sup>a</sup>	-	6	9	9	9	9
Tier 2 █ % rebate (\$)	-	4	7	8	12	12
<b>Proposed combined treatment-resistant migraine cap parameters</b>						
Specified months	Jun 21 - May 22	Jun 22 - May 23	Jun 23 - May 24	Jun 24 - May 25	Jun 25 - May 26	Jun 26 - May 27
Tier 1 combined cap (\$)	2	7	8	12	11	11
Tier 2 combined cap (\$)	2	8	11	13	14	15

Source: Table 4.7.1, p166; Table 4.7.2, pp167-168; Table 4.7.3, p168 of the resubmission; Section 4 budget impact estimates ('RSA proposal max eligible popn' worksheet).

Abbreviations: CGRP, calcitonin gene-related peptide.

<sup>a</sup> Tier 1 and Tier 2 caps based on galcanezumab uptake rates of █%, █%, █%, █% and █% in Years 2 to 6, respectively. Tier 1 cap based on █ of patients continuing at 3 months. Tier 2 cap based on █ of patients continuing at 3 months.

The redacted values correspond to the following ranges:

- <sup>1</sup> 50,000 to < 60,000
- <sup>2</sup> \$10 million to < \$20 million
- <sup>3</sup> 80,000 to < 90,000
- <sup>4</sup> \$20 million to < \$30 million
- <sup>5</sup> 60,000 to < 70,000
- <sup>6</sup> 70,000 to < 80,000
- <sup>7</sup> \$30 million to < \$40 million
- <sup>8</sup> \$40 million to < \$50 million
- <sup>9</sup> 100,000 to < 200,000
- <sup>10</sup> 90,000 to < 100,000
- <sup>11</sup> \$60 million to < \$70 million
- <sup>12</sup> \$50 million to < \$60 million
- <sup>13</sup> \$70 million to < \$80 million
- <sup>14</sup> \$80 million to < \$90 million
- <sup>15</sup> \$90 million to < \$100 million

6.71 The evaluation considered the high frequency episodic migraine portion of the cap may not be reliable due to issues with the resubmission's estimation of financial implications (as described in Table 16). Additionally, there were differences in the epidemiological approaches used to derive the numbers of chronic migraine and high frequency episodic migraine patients, which may have led to double counting of patients in the estimates. The PSCR stated it would accept the assumption that 90% of migraine patients have episodic migraine (rather than 92.39%) to address the concern regarding double counting.

6.72 The resubmission stated that the estimated volumes for high frequency episodic migraine and chronic migraine could be used to derive a weighted price for galcanezumab in treatment-resistant migraine. The derivation of the proposed weighted (effective) ex-manufacturer price of \$█ is presented in the table below.

**Table 19: Proposed galcanezumab weighted effective ex-manufacturer price**

	Year 2-6 volume	Year 1-5 volume	AEMP	Weighted AEMP
Treatment-resistant chronic migraine	█ <sup>1</sup>	-	\$█	-
Treatment-resistant high frequency episodic migraine	-	█ <sup>1</sup>	\$█	\$█

Source: Table 4.7.4, p169 of the resubmission.

Abbreviations: AEMP, approved ex-manufacturer price.

The redacted values correspond to the following ranges:

<sup>1</sup> 500,000 to < 600,000

6.73 The ESC considered a █ price for galcanezumab may be appropriate to expand the listing to include high frequency episodic migraine patients given the lower headache burden in this population. The pre-PBAC response stated a █ price for galcanezumab is not appropriate because patients with high frequency episodic migraine who have failed ≥ 3 prior preventives have a high unmet need and a significant burden of disease, with no treatment options apart from acute medication and are considered to be as disabled as those diagnosed with chronic migraine.

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

## 7 PBAC Outcome

7.1 The PBAC recommended amending the current PBS listing of galcanezumab for chronic migraine to include the treatment of patients with high frequency episodic migraine by removing the criteria for patients to have an average of 15 or more headache days per month. The resulting PBS listing for galcanezumab is for the treatment of patients who have an inadequate response, intolerance, or a contraindication to at least three prophylactic migraine medications, with 8 or more migraine headache days per month. The PBAC considered galcanezumab would be cost effective for the high frequency episodic migraine patient population at a price no higher than the current effective price for patients with chronic migraine. The PBAC considered the new patient population should be included in the chronic migraine risk share arrangement with an increase in expenditure caps.

7.2 The PBAC noted the consumer comments and acknowledged there was a clinical need for broader access to CGRP inhibitors to increase the treatment options for people with treatment-resistant high frequency episodic migraine.

7.3 The PBAC considered best supportive care was an appropriate comparator for patients with high frequency episodic migraine who have failed at least three prophylactic migraine medications.

- 7.4 The PBAC noted that the resubmission was based on the CONQUER study, the same clinical study as the submission considered in November 2020. The CONQUER study was a randomised controlled trial comparing galcanezumab 120 mg (with an additional 120 mg loading dose) to placebo (representing best supportive care) in patients with chronic and episodic migraine who have previously failed between 2 and 4 preventative treatments for migraine. The PBAC noted the clinical claim in the submission was based on patients with high frequency episodic migraine who had received 3 or 4 prior preventative medications (n=80) which was a subgroup of the ITT population (n=458). The PBAC noted for the subgroup the mean difference in the change from baseline in the number of migraine headache days per month for galcanezumab vs placebo at 12 weeks was -2.43 (95%CI: -4.08, -0.79). The PBAC considered that treatment with galcanezumab resulted in a modest reduction in the number of migraine headache days per month compared to placebo.
- 7.5 The PBAC noted the economic model in the resubmission was the same as that considered in November 2020. The PBAC recalled the ESC had previously considered the economic model was unlikely to be reliable for decision-making (para 6.60, galcanezumab PSD, November 2020 PBAC meeting) and noted that although some inputs had been updated, the model structure was unchanged and remained unreliable. However, the PBAC considered that, given the similarities in patient populations, on balance, galcanezumab was likely to be cost effective for high frequency episodic migraine at a price no higher than the price for chronic migraine.
- 7.6 The PBAC considered that, with some revisions (as outlined below), the estimated patient numbers were conservative and reasonable in the context of a risk share arrangement. The PBAC considered the following revisions to the financial estimates were appropriate:
- Apply the revised price as outlined in the paragraph above;
  - Assume a prevalence of migraine of 14.5% and 90% have episodic migraine, consistent with previous considerations of episodic and chronic migraine; and
  - Remove grandfathered patients from the financial estimates as these patients would be accounted for in the estimated prevalent population.
- 7.7 The PBAC considered the high frequency episodic migraine population should be included in the current risk share arrangement in place for chronic migraine to manage the risk of use being substantially higher than expected. The PBAC advised the financial estimates for this population (as revised in the paragraph above) should be added to the Tier 1 chronic migraine expenditure caps. The PBAC considered that, consistent with its previous recommendation for chronic migraine, it would be appropriate for the Tier 2 expenditure caps to be based on the assumption that  $\frac{1}{3}$  of patients achieve a 30% reduction in migraine headache days at the response assessment time point.
- 7.8 The PBAC advised the chronic migraine restriction criteria for galcanezumab should be amended as outlined in paragraphs 3.1, 3.5 and 3.6. The PBAC noted it would be

appropriate to flow on the change in paragraph 3.6 to the fremanezumab chronic migraine restriction criteria.

7.9 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for galcanezumab:

- a) The treatment provided a modest improvement in efficacy compared to best supportive care for some patients;
- b) The treatment is not expected to address a high and urgent unmet clinical need because there are other treatments available for migraine;
- c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.10 The PBAC noted that this resubmission is not eligible for an Independent Review.

**Outcome:**

Recommended [REDACTED]

## 8 Recommended listing

8.1 Amend existing listing as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
GALCANEZUMAB					
120 mg / 1 mL solution for injection, pre-filled pen	<a href="#">12478R</a>	2	2	1	Emgality
<b>Restriction Summary 12028 / ToC: 12064: Authority Required: Streamlined</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [ <i>amendment to existing code</i> ]					
<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.					
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.					
<b>Administrative Advice:</b> Special Pricing Arrangements apply.					
<b>Indication:</b> Treatment-resistant migraine					
<b>Treatment Phase:</b> Initial treatment					
<b>Treatment criteria:</b> Must be treated by a neurologist					

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	<b>AND</b>
	<b>Treatment criteria:</b>
	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
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have experienced at least 8 days of migraine headache days per month, over a period of at least 6 months, prior to commencement of treatment with this medicine for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
	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
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must be appropriately managed by his or her practitioner for medication overuse headache, prior to initiation of treatment with this drug
	<b>AND</b>
	<b>Population criteria:</b>
	Patient must be aged 18 years or older
	<b>AND</b>
	<b>Prescribing instructions:</b>
	Prophylactic migraine medications are propranolol, amitriptyline, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate or topiramate.
	<b>AND</b>
	<b>Prescribing instructions:</b>
	Patient must have the number of migraine headache days per month documented in their medical records.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
GALCANEZUMAB					
120 mg / 1 mL solution for injection, pre-filled pen	<a href="#">12469G</a>	1	1	5	Emgality
<b>Restriction Summary 12029 / ToC: 12029: Authority Required: Streamlined</b>					
<b>Concept ID</b>	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)				
(for internal Dept. use)	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [amendment to existing code]				
7606	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.				
7607	<b>Administrative Advice</b> No increase in the maximum number of repeats may be authorised.				
7608	<b>Administrative Advice:</b> Special Pricing Arrangements apply.				
[new]	<b>Indication:</b> Treatment-resistant migraine				
	<b>Treatment Phase:</b> Continuing treatment				
	<b>Treatment criteria:</b>				
Amend 24912	Must be treated by a neurologist or in consultation with a neurologist				

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	<b>AND</b>
	<b>Treatment criteria:</b>
27610	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
	<b>AND</b>
	<b>Clinical criteria:</b>
11364	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	<b>AND</b>
	<b>Clinical criteria:</b>
25161	Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine days per month
	<b>AND</b>
	<b>Clinical criteria:</b>
25163	Patient must continue to be appropriately managed for medication overuse headache
	<b>AND</b>
	<b>AND</b>
	<b>Prescribing instructions:</b>
26201	Patient must have the number of migraine days per month documented in their medical records.

8.2 Amend item as follows:

The amendment to concept id 24912 above should be flowed to PBS item code 12611R (continuing restriction criteria for fremanezumab).

***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

The sponsor had no comment.