

6.05 GALCANEZUMAB, Injection 120 mg in 1 mL pre-filled pen, Emgality[®], Eli Lilly Australia Pty Ltd.

1 Purpose of submission

- 1.1 The submission requested an Authority Required (Streamlined) listing for galcanezumab for the treatment of episodic migraine in patients who have experienced an inadequate response, intolerance, or a contraindication to at least three prophylactic migraine medications.
- 1.2 The submission requested listing on the basis of a cost-utility analysis versus placebo/best supportive care (BSC). The key components of the clinical issue addressed in the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adult patients with episodic migraine (up to 14 headache days per month, with at least 4 migraine headache days) who have experienced an inadequate response, intolerance or a contraindication to at least three 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	Monthly migraine headache days, use of acute headache medication, quality of life, adverse events
Clinical claim	In patients with treatment-resistant episodic migraine, galcanezumab is superior in terms of efficacy and similar in terms of safety compared to best supportive care

Source: Table 1.1.1 of the 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 considerations

- 2.2 This was the first consideration of galcanezumab for episodic migraine.
- 2.3 Galcanezumab was recommended by the PBAC in July 2019 for the treatment of chronic migraine (≥ 15 headache days per month of which ≥ 8 are migraine headache days) who have experienced an inadequate response, intolerance or a contraindication to ≥ 3 prophylactic migraine medications. It was not PBS listed at the time of consideration of this submission. A minor resubmission for chronic migraine to amend the cost-minimisation basis, financial estimates and risk sharing

arrangement details from the July 2019 recommendation was considered at the November 2020 at meeting (refer to agenda item 7.08).

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
Initial –loading dose					
GALCANEZUMAB 120 mg / 1 mL solution for injection, pre-filled pen	2	2	01	\$TBC (published) \$██████ (effective)	Emgality®, Eli Lilly Australia Pty Ltd
Initial					
GALCANEZUMAB 120 mg / 1 mL solution for injection, pre-filled pen	4	4	4	\$TBC (published) \$██████ (effective)	Emgality®, Eli Lilly Australia Pty Ltd
Continuing					
GALCANEZUMAB 120 mg / 1 mL solution for injection, pre-filled pen	1	1	5	\$TBC (published) \$██████ (effective)	Emgality®, Eli Lilly Australia Pty Ltd

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Condition:	<i>Treatment-resistant episodic migraine</i>
Restriction:	<input checked="" type="checkbox"/> Authority Required (Streamlined)
Treatment criteria:	Must be treated by a neurologist.
Treatment phase:	Initial - loading dose <i>treatment covering the loading dose and doses at week 4 and week 8</i>
Clinical criteria:	<p>Patient must have experienced an average of 14 or less headache days per month, with at least 4 days of migraine, over a period of at least 6 months, prior to commencement of treatment with <i>this medicine for this condition galcanezumab</i>,</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 <i>this medicine for this condition galcanezumab</i>.</p> <p>AND</p> <p><i>Patient must be appropriately managed for medication overuse headache, prior to initiation of treatment with this medicine for this condition</i></p> <p>AND</p> <p><i>Patient must not have previously received PBS-subsidised treatment with this drug for this condition</i></p>
Population criteria:	Patient must be aged 18 years or older.
Prescriber Instructions:	<p>Prophylactic migraine medications are propranolol, amitriptyline, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate or topiramate.</p> <p><i>Patient must have a baseline measurement of the number of migraine days per month documented in their medical records.</i></p>
Treatment phase:	Initial
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND

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	<p>Patient must have experienced an average of 14 or less headache days per month, with at least 4 days of migraine, 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>
Population criteria:	Patient must be aged 18 years or older.
Prescriber Instructions:	Prophylactic migraine medications are propranolol, amitriptyline, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate or topiramate.
Treatment phase:	Continuing
Treatment criteria:	Must be treated by a neurologist or
	<i>Must be treated by a physician who has consulted a neurologist</i>
Clinical criteria:	<p>Patient must have previously received PBS-subsidised 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 headache days per month in order to be eligible for continuing PBS-subsidised treatment</p> <p>AND</p> <p><i>Patient must continue to be appropriately managed for medication overuse headache</i></p>
Prescriber Instructions:	<i>Patient must have a baseline measurement of the number of migraine days per month documented in their medical records.</i>
Treatment phase:	Grandfathering
Clinical criteria:	<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 an average of 14 or less headache days per month, with at least 4 days of migraine, 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 headache days per month in order to be eligible for continuing PBS-subsidised treatment</p>

Source: Table 1.4.1.; Table 1.4.2; Table 1.4.3; Table 1.4.4; Table 1.4.5 of the submission

Notes: Published price to be confirmed by sponsor once a special pricing agreement is determined, consistent with that requested previously for the chronic migraine indication

- 3.2 A special price arrangement was requested for galcanezumab and no published price was provided in the submission. The ESC noted the proposed effective price for episodic migraine (approved ex-manufacturer price (AEMP) of \$ [REDACTED]) was higher than the price recommended by the PBAC for the chronic migraine population (AEMP of ~\$ [REDACTED]) in July 2019. The ESC considered a higher price for a population with less severe disease and a lower incremental benefit had not been adequately justified.
- 3.3 The requirement for patients to have experienced up to 14 headache days per month was proposed to ensure that the restriction for episodic migraine does not overlap with the PBAC-recommended restriction for chronic migraine (an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months). However, there may be people who would benefit from treatment

who do not qualify under either restriction. For example, someone with at least 15 headache days per month but between 4 and 8 migraine days. Such a distinction between chronic and episodic migraine is not in alignment with the TGA indication or published guidelines which generally suggest prophylactic treatment for patients who have experienced an average of at least 4 migraine headache days (MHD) per month. The ESC noted that episodic and chronic migraine is on a continuum rather than discrete categories, and as such, patients may frequently cycle between chronic and episodic migraine. The ESC considered a single listing for treatment-resistant migraine may be more appropriate, rather than separate listings for episodic and chronic migraine.

- 3.4 The proposed continuation criteria for the PBS listing of galcanezumab in treatment-resistant episodic migraine population was that the 'patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine headache days per month.' However although implied by the duration of coverage provided by the maximum quantity and repeats stated in the Initial treatment phase (12 weeks), the minimum timing of response assessment was unstated, meaning that a prescriber could apply for continuing treatment at any time point. The ESC considered a criterion stating the minimum treatment duration needing to have elapsed prior to applying for continuing treatment would be appropriate.
- 3.5 There is a significant risk of use outside of the proposed restriction among patients who do not meet the required response under the continuation criteria but who have experienced an improvement in migraine symptoms on galcanezumab.
- 3.6 There is a paucity of evidence on the optimal duration of treatment, or on patients restarting treatment after a break. Although patients may discontinue treatment due to poor tolerability or lack of efficacy, patients who experience an improvement are also unlikely to remain on treatment indefinitely.

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

4 Population and disease

- 4.1 Migraine is a distinct neurological disease characterised by recurrent often unilateral, throbbing head pain (moderate or severe in intensity) and a number of sensory and dysautonomic symptoms including nausea, vomiting, photophobia (sensitivity to light) or phonophobia (aversion to loud sounds). Due to these symptoms, patients report substantial impairment in their ability to perform daily or physical activities, attend school/work and function socially. Migraine is considered a spectrum disorder, typically characterised by the frequency of migraine days per month. Episodic migraine is defined as fewer than 15 headache days per month, with 4- 8 consisting of typical migraine days.
- 4.2 The submission specified the clinical place of galcanezumab as last line treatment, after a patient has failed to achieve an adequate response to at least three migraine

oral prophylactic medications, or is intolerant to, or contraindicated for, the available migraine prophylactic medications.

- 4.3 Galcanezumab is a humanised monoclonal antibody (IgG4) that binds the calcitonin gene-related peptide (CGRP). The recommended dose of galcanezumab is 120 mg injected subcutaneously once monthly, with a 240 mg loading dose as the initial dose.

5 Comparator

- 5.1 The proposed comparator is best supportive care, consisting of no further prophylaxis but with continuation of acute headache pain medications as required. The *ESC noted the* PBAC previously accepted that best supportive care was the appropriate comparator for patients who have failed at least three lines of preventive therapy in chronic migraine and epilepsy (item 6, topiramate Public Summary Document (PSD), March 2007 PBAC meeting; item 6, Botox PSD, July 2013 PBAC meeting; paragraph 5.2, erenumab PSD, March 2019 PBAC meeting). Preventive therapies for migraine include beta-blockers, amitriptyline, venlafaxine, sodium valproate, and topiramate.

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 (48), health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described the debilitating physical, mental and social impact of episodic and chronic migraine and the range of potential benefits of treatment with galcanezumab and the other CGRP inhibitors. Many patients expressed their concern at not being able to afford the medicine if it was not listed on the PBS, and many comments noted that their free access to the medicine on various programs had now ended. Benefits of treatment included a reduction in the number and severity of migraines, improvement in quality of life, the ability to return to work and easier administration compared to Botox. Many comments described immediate improvements after commencing treatment with a CGRP inhibitor, but if treatment was stopped, then these improvements ceased. Quality of life improvements included pain relief, more functional capacity, and capacity to interact with others socially and in the workplace. Some of the comments outlined the large number of different medications patients have used to treat their migraines with little relief provided or unacceptable side effects.
- 6.3 The PBAC noted the advice received from Migraine Australia that they believed that the terms ‘chronic’ and ‘episodic’ should be abandoned for general discussion of migraine. They noted that these terms have conflicting meanings in the patient community, and believed that the terminology that should be used in place of episodic

and chronic is ‘manageable’ and ‘difficult to manage’. Reductions in frequency of attacks by those who responded to the treatments was also noted, and affordability issues in regards to equity of access currently across Australia.

Clinical trial

6.4 The submission was based on one head-to-head trial comparing galcanezumab 120 mg (with an additional 120 mg loading dose at initiation) to placebo (n=462; CONQUER) in patients with chronic and episodic migraine, who had previously failed between 2 and 4 preventive treatments for migraine.

6.5 The comparison between galcanezumab and placebo/BSC was based on three trial populations within CONQUER: the intention to treat (ITT) population, the episodic migraine subpopulation (n=269), and the episodic migraine subpopulation with ≥3 prior preventive treatments (n=100). The episodic migraine subpopulation with ≥3 prior preventive treatments was selected to correspond to the proposed PBS population, which includes patients who had failed, were intolerant or were contraindicated to ≥3 prophylactic medications.

6.6 Details of the trial presented in the submission are provided in the table below.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
CONQUER	CGAW Clinical Study Report: A randomised, 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	September 2019
	CGAW Clinical Study Report Addendum: A randomised, double-blind, placebo-controlled study of galcanezumab in adults with treatment-resistant migraine – the CONQUER study. Final results from the open-label treatment phase	December 2019
	Mulleners, W., 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): p. 128.
	Maizels, M., et al., Assessment of anxiety and depression in a randomised, 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): p. 129-130.

Source: Table 2.2.1, p.55 of the submission

6.7 The key features of the CONQUER randomised trial are summarised in the table below. As the subgroup analysis presented in the submission formed the basis of the clinical claim in the PBS population, and treatment effects in this subpopulation informed the economic evaluation, information relative to the subgroup is included in the table.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome	Use in modelled evaluation
Galcanezumab versus placebo						
CONQUER	462 (subgroup = 100)	Randomised, double blinded, multi centre, 12 week duration	Low	Failed ≥3 prophylactic medication classes	Change from baseline in monthly migraine headache days	≥50% responder for change in migraine days; change from baseline in migraine headache days

Source: Table 2.4.3, p.66; Table 2.3.1, p.57 of the submission

- 6.8 The episodic migraine ≥3 prior treatment failures subgroup presented was small (n=100), and therefore results based on this subgroup should be interpreted with caution.
- 6.9 The episodic migraine subpopulation with ≥3 prior treatment failures in the CONQUER trial had relatively severe disease, with high monthly MHD at baseline (approximately 10 per month on average) and with a majority of patients (80%) diagnosed with high frequency episodic migraine, defined as 8 to <15 MHD per 30-day period. The ESC noted a higher proportion of patients in the galcanezumab treatment arm in the subpopulation had high frequency episodic migraine compared to the placebo arm (85% vs 72%, respectively). The ESC considered it was unclear whether disease severity in the trial would be similar in the proposed PBS population who are required to have 4 or more MHDs.
- 6.10 The episodic migraine with ≥3 prior treatment failure subpopulation included patients with 3 or 4 prior preventive medication category failures due to inadequate efficacy or safety/tolerability (as based on a subjective assessment by investigators at trial sites); the proposed restriction specifies patients who have experienced an inadequate response, intolerance or a contraindication to at least three prior preventive migraine medications (within or between categories). Therefore, the PBS population may be more treatment naïve (or treatment experienced, in the case of those with more than 4 prior medications) than the trial subpopulation. The ESC noted patients with episodic and chronic migraine often cycle through prophylactic medications, depending on the severity of disease at a given time.
- 6.11 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.
- 6.12 The placebo arm of the CONQUER trial may not be a suitable proxy for best supportive care. While patients in the trial were allowed to use acute medicines for the treatment of migraines, they were not permitted to use any other prophylactic medications during the trial. The evaluation considered this may not reflect the management of patients in the PBS population. The ESC considered that, as galcanezumab was

positioned as a last line treatment for migraine, the placebo arm of the CONQUER trial was a reasonable proxy for best support care.

- 6.13 EVOLVE-1 and EVOLVE-2 were both Phase III, multicentre, randomised, double-blind, placebo-controlled studies of galcanezumab in patients with episodic migraine, including naïve as well as treatment-resistant migraine patients. Both trials excluded patients who had failed to have an efficacy response to ≥ 3 classes of migraine preventive treatments, and therefore the submission excluded these trials from the clinical evaluation of galcanezumab. A pooled analysis of the EVOLVE trials was used in the economic model to inform the distributions of monthly MHD and the time taken to return to a treatment effect equivalent to baseline following discontinuation of galcanezumab.
- 6.14 Study CGAJ was a long-term, open-label safety study of galcanezumab in patients with migraine, including episodic and chronic migraine. A total of 270 patients were randomised to either galcanezumab 120 mg or galcanezumab 240 mg. Results were not disaggregated by migraine type, and therefore the submission excluded this study. However, CGAJ presents the longest available clinical data of galcanezumab for the treatment of migraine (12 months). The submission stated that results from the CGAJ study demonstrate longer term efficacy and safety/tolerability of galcanezumab. Results from the CGAJ publication (Camporeale et al., 2018) were used in the economic model to inform the probability of discontinuing treatment with galcanezumab due to adverse events.

Comparative effectiveness

- 6.15 Results of the comparison between galcanezumab and placebo from the CONQUER trial in the ITT population and the episodic migraine subpopulation, for the primary outcome (reduction in MHD) and proportion of the population achieving $\geq 50\%$, $\geq 75\%$, $\geq 100\%$, and $\geq 30\%$ reduction in migraine days, are summarised in Table 4.

Table 4: 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)	
Change from baseline in number of monthly migraine headache days					
Double blind treatment phase (12 weeks; galcanezumab versus placebo)					
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 Model estimated rate (SE)		Placebo Model estimated rate (SE)		OR (95%CI)
Estimated proportion of ≥50%, ≥75% and 100% responders for migraine headache days					
ITT population					
≥50% responders	37.7 (2.5)		13.3 (1.8)		3.94 (2.72, 5.69)
≥75% responders	14.5 (2.0)		3.3 (1.1)		5.01 (2.35, 10.68)
100% responders	4.9 (1.4)		0		NE
Episodic migraine subpopulation					
≥50% responders	41.8 (3.2)		17.1 (2.5)		3.48 (2.25, 5.38)
≥75% responders	18.4 (2.5)		3.7 (1.5)		5.88 (2.37, 14.55)
100% responders	7.7 (1.9)		0		NE
≥30% responders	60.7 (NR)		32.5 (NR)		NR

Source: Table 2.5.1, p.73 of the submission Table CGAW.14.37, p.364; Table CGAW.14.43, p.375 Attachment 3.1_CONQUER CSR; Table CGAW.14.7, p.141; Table CGAW.14.8, p.143 Attachment 3.2 CONQUER CSR OLE; Attachment 4.1 Galcanezumab Section 3 model (response tab)

Abbreviations: CI, confidence interval; ITT, intention to treat; LS, least squares; NE, not estimable; NR, not reported; OR, odds ratio; SE, standard error

- 6.16 The analyses showed statistically significant advantages for treatment with galcanezumab compared to placebo across all outcomes presented.
- 6.17 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. The Pre-Sub-Committee Response (PSCR) noted that the point estimates for the change in MHD were broadly similar across the ITT population and the EM subgroups with a clinically important reduction of 2 to 3 MHD. The PSCR stated that an upper confidence interval of 1.72 days is close to the MCID and the confidence intervals are wider for this analysis due to the smaller sample size.
- 6.18 The submission also presented results for the open-label extension (12 weeks) of the CONQUER trial. This showed that for both the ITT and the episodic migraine population, the prior galcanezumab (in the double-blind phase) treatment group maintained the improvement from the double-blind treatment phase in terms of mean reduction in migraine days, and the prior placebo treatment group achieved a reduction of approximately 4 MHD in the first month after initiation of galcanezumab.
- 6.19 In the EVOLVE trials treatment with galcanezumab 120 mg and 240 mg was associated with a greater overall mean reduction in monthly MHDs (4.2 to 4.7 days) compared with placebo (2.3 to 2.8 days) during the 6-month double-blind treatment phase. Galcanezumab 120 mg and 240 mg were both statistically significantly superior to placebo in the mean percentage of patients with ≥50%, ≥75%, and 100% reduction from baseline in monthly MHDs during the 6-month treatment phase.

- 6.20 In the 12 month open-label study CGAJ, for the treatment group who received galcanezumab 120 mg, the overall mean reduction from baseline in the number of monthly MHD averaged over the 12-month treatment phase was 5.6 days. The mean percentage of patients with a $\geq 50\%$ reduction in the number of monthly MHD was 65.6%. 48.5% of patients maintained 50% response for at least 6 months while 24.2% maintained their 50% response for at least 12 months. Of the 135 patients who received galcanezumab 120 mg, 7 patients discontinued the open-label phase due to an adverse event. Given that results for the episodic migraine subpopulation were not available for this study, and patients who had previously failed to have an efficacy response to ≥ 3 classes of migraine preventive treatments were excluded, results from study CGAJ are unlikely to be representative of the proposed Australian PBS population.
- 6.21 The economic model presented in Section 3 of the submission included a sensitivity analysis at a response rate of $\geq 30\%$. The data source for the $\geq 30\%$ responder analysis was not provided with the submission, and could not be verified during the evaluation.
- 6.22 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 are summarised in Table 5.

Table 5: Migraine-specific quality of life questionnaire (MSQ) and the migraine disability assessment score (MIDAS) at month 3 in CONQUER, ITT and EM population

	N	Galcanzumab LS Mean (SE)	N	Placebo LS Mean (SE)	Difference vs placebo (95%CI)
ITT population					
Change from baseline in MSQ Total Score ^a	223	21.67 (1.26)	222	10.08 (1.25)	11.59 (8.50, 14.68)
Change from baseline in MSQ Role Function-Restrictive Domain Score ^a	223	23.21 (1.35)	222	10.68 (1.34)	12.53 (9.19, 15.87)
Change from baseline in MSQ Role Function-Preventive Domain Score ^a	223	17.53 (1.20)	222	7.68 (1.19)	9.85 (6.91, 12.79)
Change from baseline in MSQ Emotional Function Domain Score ^a	223	24.02 (1.61)	222	12.02 (1.60)	12.00 (8.01, 16.00)
Change from baseline in MIDAS Total Score ^b	228	-21.10 (3.32)	225	-3.30 (3.28)	NR
Change from baseline in EQ-5D-5L Health State Index (UK weights) ^c	227	0.017 (0.01)	225	-0.001 (0.01)	NR
Change from baseline in EQ-5D-5L VAS score ^d	227	3.376 (1.31)	225	-0.086 (1.29)	NR
Episodic migraine subpopulation					
Change from baseline in MSQ Total Score ^a	137	21.70 (1.66)	132	10.91 (1.67)	10.79 (6.75, 14.83)
Change from baseline in MSQ Role Function-Restrictive Domain Score ^a	137	23.39 (1.79)	132	11.88 (1.80)	11.51 (7.14, 15.89)
Change from baseline in MSQ Role Function-Preventive Domain Score ^a	137	18.44 (1.55)	132	8.94 (1.56)	9.49 (5.73, 13.26)
Change from baseline in MSQ Emotional Function Domain Score ^a	137	22.52 (2.06)	132	11.58 (2.08)	10.94 (5.82, 16.06)
Change from baseline in MIDAS Total Score ^b	136	-18.96 (3.63)	128	-2.58 (3.68)	NR
Change from baseline in EQ-5D-5L Health State Index (UK weights) ^c	135	0.01 (0.01)	128	-0.01 (0.01)	NR
Change from baseline in EQ-5D-5L VAS score ^d	135	2.90 (1.63)	128	-0.829 (1.63)	NR

Source: Table 2.5.3, pp.76-77 of the submission; Table CGAW.14.85, p.475-477; Table CGAW.14.87, p.480-482 of Attachment 3.1 CONQUER clinical study report

Abbreviations: CI, confidence interval; EQ-5D-5L, European Quality of Life 5-Dimensions 5-Levels; ITT, intent-to-treat; LSMean, least square mean; MSQ, migraine-specific quality of life questionnaire; MIDAS, migraine disability assessment score; NR, not reported; SE, standard error; VAS, visual analogue scale

^a Baseline values are for the entire ITT or EM population. Each of the domains and the total score are measured on a scale of 0 to 100, with a higher score indicating better health status

^b Baseline is defined as the last measure before the first dose date. Scores range from 0 to 270, with a higher score indicating more disability

^c Baseline is defined as the last measure before the first dose date. Health utility provides a single value on a scale from less than 0 to 1. Negative values are valued as worse than dead, 0 is a health state equivalent to death, 1 is a health state equivalent to perfect health

^d Baseline is defined as the last measure before the first dose date. Patient rates their perceived health state from 0 (the worst health you can imagine) to 100 (the best health you can imagine)

6.23 There was a statistically significant greater mean improvement from baseline on the MSQ total score and all domain scores in the galcanzumab treatment group compared with placebo. Similarly, there was a statistically significantly greater mean reduction in perceived migraine-related disability (MIDAS total score) at month 3 for patients in the galcanzumab treatment group compared with the placebo group. There was no statistically significant change from baseline in the EQ-5D in either treatment group.

6.24 Table 6 summarises the efficacy results for the subgroup of patients with episodic migraine who had failed ≥ 3 preventive migraine medications in the CONQUER trial.

Table 6: Efficacy results for episodic migraine ≥3 treatment failures subpopulation in the CONQUER trial

	Galcanezumab N=56	Placebo N=44	Difference (95% CI)
Change from baseline in number of monthly migraine headache days, LS mean (SE)	-3.64 (0.59)	-0.65 (0.68)	-2.99 (-4.53, -1.45)
≥50% responders, model estimated proportion (SE)	41.1 (4.9)	16.5 (4.1)	OR: 3.53 (1.71, 7.25)
≥30% responders (proportion from model)	61.1	29.0	NR
Change from baseline in MSQ Role Function-Restrictive Domain Score at Month 3, LS mean (SE)	22.73 (3.41)	14.50 (3.55)	8.23 (0.28, 16.17)

Source: Table 2.6.3 of the submission; Attachment 4.1 Galcanezumab Section 3 model (parameter tab; response tab)

Abbreviations: CI, confidence interval; ITT, intention to treat; LS, least squares; NR, not reported; OR, odds ratio; SE, standard error

6.25 Consistent with the results of the overall trial population, the subgroup analyses showed statistically significant advantages for galcanezumab compared to placebo across all outcomes presented.

6.26 The point estimates for change from baseline in MHD for the subgroup were numerically lower than for the full trial population, however this is likely to reflect the inclusion of patients with chronic migraine in the ITT population, who may achieve larger absolute reductions in monthly migraine days. The upper confidence interval for the change in monthly migraine days (-1.45 days) was less than the proposed MCID of at least 2 days.

Comparative harms

6.27 Adverse events reported in the overall trial population of the CONQUER trial are summarised in Table 7.

Table 7: Summary of key adverse events in the trials (ITT population)

	Galcanezumab n with event/N (%)	Placebo n with event/N (%)
Overall summary of adverse events		
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
Deaths, n (%)	0	0
Summary of most frequently reported treatment emergent adverse events		
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 2.5.6, p.80; Table 2.5.7, p.81 of the submission

- 6.28 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.
- 6.29 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.
- 6.30 The submission did not address potential concerns around the use of CGRP inhibitors and risk of cardiovascular events. The evaluation noted that there are theoretical concerns suggesting that interfering with CGRP could modify processes relevant to protection against ischaemia, increasing the risk of cardiovascular events. CONQUER excluded patients with abnormal electrocardiogram, patients at serious cardiovascular risk, or those with a history of clinically significant cardiovascular disease.
- 6.31 Safety results comparing galcanezumab and placebo based on the episodic migraine ≥ 3 prior treatment failures subpopulation are summarised in Table 8.

Table 8: Summary of adverse events in the double-blind treatment phase of CONQUER, episodic migraine ≥ 3 treatment failure subgroup

	Galcanezumab n with event/N (%)	Placebo n with event/N (%)
Treatment emergent adverse events, n (%)	30/56 (53.57)	22/44 (50.00)
Serious adverse events, n (%)	2/56 (3.57)	0
Discontinuation related to adverse events, n (%)	0	0
Deaths, n (%)	0	0

Source: Table 2.6.4, p.89 of the submission

- 6.32 The overall incidence of adverse events was similar between treatment arms. There was a slightly greater incidence of serious adverse events in the galcanezumab treatment group. A description of serious adverse events in the episodic migraine ≥ 3 treatment failure subgroup was not provided.
- 6.33 A more detailed description of adverse events and discontinuations in the episodic migraine ≥ 3 treatment failure subgroup was not included in the submission. It is unclear whether compliance with treatment will be the same in the population with ≥ 3 previous treatment failures as in the overall population.

Benefits/harms

- 6.34 On the basis of the direct evidence presented in the submission (12 weeks of double-blind treatment in CONQUER), for every 100 patients treated with galcanezumab 120 mg monthly in comparison to placebo:
- Approximately 25 more patients would have a $\geq 50\%$ reduction in monthly migraine days.
 - Patients would experience, on average, approximately 2 to 3 fewer migraine days per month.

- Approximately 3 patients would experience skin redness where the injection was given.

The efficacy of galcanezumab was similar in the ITT population and in the subgroup populations (EM and EM with ≥ 3 prior treatment failures).

Clinical claim

- 6.35 The submission claimed that galcanezumab, in patients with treatment-resistant episodic migraine, is superior to best supportive care in terms of efficacy and with similar safety and tolerability.
- 6.36 While galcanezumab demonstrated a statistically significant advantage over placebo for the key outcomes of reduction in migraine days per month and $\geq 50\%$ responder rate, and was generally well tolerated during the CONQUER trial, the evaluation considered there are a number of outstanding issues associated with this comparison.
- 6.37 The episodic migraine subpopulation with ≥ 3 prior treatment failures in the CONQUER trial had relatively severe disease, with high monthly MHD at baseline (approximately 10 per month on average) and with a majority of patients (80%) diagnosed with high frequency episodic migraine, defined as 8 to < 15 MHD per 30-day period. The ESC considered it was unclear whether disease severity in the trial would be similar in the proposed PBS population who are required to have 4 or more MHD.
- 6.38 The placebo arm of the CONQUER trial may not be a suitable proxy for best supportive care. While patients in the trial were allowed to use acute medicines for the treatment of migraines, they were not permitted to use prophylactic medications during the trial. The evaluation considered this may not reflect the management of patients in the PBS population. The ESC considered that, as galcanezumab was positioned as a last line treatment for migraine, the placebo arm of the CONQUER trial was a reasonable proxy for best support care and this had been previously accepted by the PBAC for other medicines for migraine (paragraph 5.1).
- 6.39 The CONQUER trial assessed outcomes at 12 weeks, and there remains uncertainty in any durability of effects and adverse events resulting from prolonged use. Some concerns exist about the long-term effects of continuous blocking of CGRP or its receptor due to CGRP's cardiovascular protective role. Given that galcanezumab is expected to be a chronic treatment, with patients likely to take galcanezumab for a long duration (> 1 year), studies with longer follow-up are needed.
- 6.40 There is a paucity of evidence on the optimal duration of treatment. Although patients may discontinue treatment due to poor tolerability or lack of efficacy, patients who experience an improvement are also unlikely to remain on treatment indefinitely.
- 6.41 The therapeutic conclusion in the ≥ 3 treatment failure subgroup was based on an analysis of limited subgroup data. Further, this prespecified subpopulation included patients with 3 or 4 prior preventive medication category failures due to inadequate efficacy or safety/tolerability (as based on a subjective assessment by investigators at trial sites); the proposed restriction specifies patients who have experienced an

inadequate response, intolerance or a contraindication to at least three prior preventive migraine medications (within or between categories). Therefore, the PBS population may be less treatment experienced more treatment naïve (or more treatment experienced, in the case of those with more than 4 prior medications) than the trial subpopulation.

- 6.42 The ESC considered the claim that galcanezumab, in patients with treatment-resistant episodic migraine, is superior to best supportive care in terms of efficacy was supported. The ESC considered galcanezumab appeared reasonably well tolerated and the claim of non-inferior safety compared to best supportive may be reasonable but noted the lack of long term safety data. The PBAC agreed with the ESC that the clinical claims were supported by the clinical data presented but noted the benefit was modest and may not be realised in the population proposed for PBS listing.

Economic analysis

- 6.43 The submission presented a cost-utility analysis based on the within-trial comparison of galcanezumab and placebo, with placebo as a proxy for best supportive care.
- 6.44 A summary of the model structure is presented in Table 9.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
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 double blind treatment period 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 (≥ 3 treatment failure episodic migraine subgroup) Mean migraine headache days modelled from the observed migraine headache day distributions in the CONQUER and EVOLVE 1 and 2 trials Return to baseline migraine headache days informed by washout data in the EVOLVE trials Discontinuation due to adverse events from CGAJ open-label study Background mortality using annual age-specific mortality (ABS life tables)
Utilities	Utility values mapped from the MSQ in CONQUER to EQ-5D-3L using an algorithm published by Gillard et al. (2012). The ESC noted a mixed model regression analysis of the transformed utilities was used to determine the utility gain applied in the economic model, rather than a direct mapping.
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: Table 3.3.1 of the submission

6.45 A summary of the key drivers of the economic model is presented in Table 10 below.

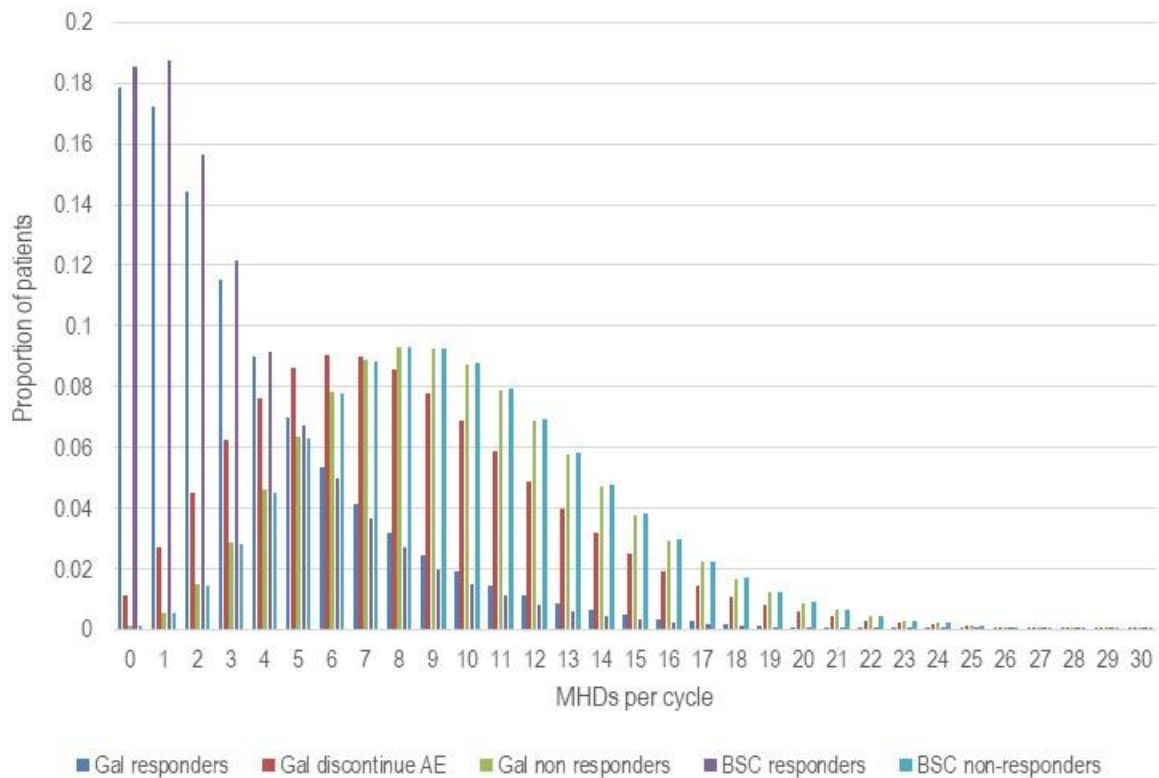
Table 10: Key drivers of the model

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 (41.1% in the galcanezumab treatment arm). There is a risk that a higher proportion of patients will continue treatment, who still achieve a meaningful 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 impact of a higher proportion of patients with lower response rates and a lower reduction in mean MHDs was unable to be adequately assessed in sensitivity analysis due to the structure of the model, however this represents a likely scenario in clinical practice, particularly if patients in the PBS population do not have the high MHDs observed at baseline in the CONQUER trial and modelled in the submission. 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
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. This also assumed that the response to galcanezumab is maintained long-term. Current evidence from a 12-month open label study (CGAJ) did not adequately demonstrate the maintenance of treatment effect, with only 24% of $\geq 50\%$ responders maintaining this response a 12 months.	High, favours galcanezumab
Utilities	The utility values were based on mapping of the MSQ in a subgroup of patients with episodic or chronic migraine with ≥ 3 treatment failures from the CONQUER trial to EQ-5D-3L. The data used in the analysis were not well documented, and the derived utility values could not be adequately evaluated. 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). The ESC noted mapped utilities were used in a regression analysis to derive a utility improvement of 0.0573 for all galcanezumab health states compared to BSC. An improvement in utility associated with galcanezumab treatment independent of the number of monthly migraine days was applied in the model, meaning that patients experiencing the same number of monthly migraine days had higher utilities when treated with galcanezumab. This may duplicate the benefit of treatment in the model. Applying pooled utility values or 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 submission

- 6.46 Patients enter the model with an average of 9.89 MHD per month (baseline). After 3 months of treatment, patients who achieve a $\geq 50\%$ reduction in migraine days experience an average of 3.29 MHD for galcanezumab-treated patients and 2.90 MHD 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 MHD (-1.71 for galcanezumab; 0.83 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 MHD over 13 months.
- 6.47 Modelled distributions were based on the placebo group in the EVOLVE studies. The average modelled distributions of MHDs used in the economic model are summarised in Figure 1.

Figure 1: Mean predicted distributions of migraine headache days per cycle by health state



Source: Constructed during the evaluation using Attachment 4.1 Galcanezumab Section 3 model

- 6.48 The modelled mean distributions over a 5-year time horizon highlight the low MHDs associated with responder health states, most of whom achieved 0, 1, or 2 MHDs per cycle. Patients who discontinued galcanezumab due to an adverse event, and non-responders in both arms accrued more MHDs in each cycle. Given that costs and outcomes applied in the model were driven by these distributions, any change in these is likely to affect the ICER.
- 6.49 The modelled distributions include people with MHDs that would be outside of the restriction. At baseline in the economic model, 4.9% of the population experiences 0-3 MHDs, and 14.8% of the population experiences ≥ 15 MHDs.
- 6.50 The utilities applied in the model are summarised in Table 11 below.

Table 11: Average utility estimates in the economic model

Health state/cycle	Galcanezumab	BSC	Source
Prior to response assessment			
On treatment			Based on distribution of headache days associated with baseline migraine headache days per month (9.89); multiplied by corresponding baseline utilities in cycle 1; and by response utilities (which vary by treatment arm) in cycles 2 and 3
- Cycle 1	0.5997	0.5997	
- Cycle 2-3	0.6873	0.6300	
Off treatment (adverse event)			Based on distribution of headache days associated with baseline migraine headache days per month (9.89); multiplied by baseline utilities
- Cycles 2-3	0.5997	0.5997	
After response assessment			
On treatment			Based on distribution of headache days associated with mean migraine headache days per month for responders (3.29 for galcanezumab; 2.90 for BSC); multiplied by corresponding response utilities (which vary by treatment arm)
- Cycles 4+	0.7618	0.7089	
Off treatment (non-response)			For cycle 4, based on distribution of headache days associated with mean migraine headache days per month for non-responders (8.18 for galcanezumab; 10.72 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 (9.89). Migraine days are multiplied by corresponding baseline utilities
- Cycle 4	0.6257	0.5871	
- Cycle 5+	0.5997	0.5997	
Off treatment (adverse event)			Varies by cycle according to assumed waning of treatment effect over 13 cycles following discontinuation. Mean migraine headache days per month varies from 6.16 to 10.02. Baseline utilities applied.
- Cycles 4+	0.5977- 0.6565	-	

Source: constructed during the evaluation using A4.1_Galcanezumab_Section 3 Model Excel spreadsheet provided with the submission
Abbreviations: BSC, best supportive care

6.51 There was a large utility benefit associated with being on galcanezumab treatment, both compared with baseline/off-treatment values (ranging from 0.049 for 0 MHD to 0.166 for 30 MHD), and compared with those on-treatment in the BSC arm (a constant 0.0573), meaning that patients experiencing the same number of MHD had higher utilities if treated with galcanezumab (Table 12). The ESC considered application of these higher utilities to the galcanezumab ‘on-treatment’ health state was not adequately justified, and the model was sensitive to the use of these utilities.

Table 12: Utility values applied in the economic model base case

No. of MHD per month	Treatment specific utility values (base case)				
	On-treatment			Off-treatment	
	GAL	BSC	Increment (GAL – BSC)	Baseline	Increment (GAL – off-treatment)
0	0.7990	0.7417	0.0573	0.7500	0.0490
1	0.7877	0.7304	0.0573	0.7348	0.0529
2	0.7764	0.7191	0.0573	0.7196	0.0568
3	0.7651	0.7078	0.0573	0.7044	0.0607
4	0.7538	0.6965	0.0573	0.6892	0.0646
.....					
15	0.6295	0.5722	0.0573	0.5220	0.1075
.....					
20	0.5730	0.5157	0.0573	0.4460	0.1270
.....					
25	0.5165	0.4592	0.0573	0.3700	0.1465
....					
30	0.4600	0.4027	0.0573	0.2940	0.1660

Abbreviations: BSC, best supportive care; GAL, galcanezumab; MHD, migraine headache days

- 6.52 The utility values were based on a subgroup analysis of patients with episodic or chronic migraine with ≥ 3 treatment failures from the CONQUER trial, which was stated to provide insufficient numbers of patients for robust analysis. The data used in the analysis were not well documented, and the derived utility values could not be adequately evaluated.
- 6.53 The submission stated that when stratified by treatment, the modelled utilities suggest some improvement in mapped MSQ utilities associated with treatment with galcanezumab, independent of the number of monthly MHD. The submission claimed that this suggests treatment effect may have a benefit beyond reducing the number of monthly MHD, including both headache severity and other aspects such as nausea and cognitive function. The ESC noted no evidence was provided to support this argument. Based on this, different utilities for galcanezumab and best supportive care were included in the economic base case. The ESC considered it was unclear whether the application of a utility benefit for being on treatment with galcanezumab compared with BSC was appropriate, and likely double counts the benefit of treatment in the model. The scatterplot of mapped MSQ utilities by treatment shows wide variability, with each MHD informed by a relatively small number of observations. The model was sensitive to the use of on-treatment utilities. The PSCR argued that it is reasonable that the utility values applied in the model are separated for patients on galcanezumab treatment and best supportive care in the 'on treatment' health state. The PSCR stated the submission presented a range of outcomes from the CONQUER study that supported this assumption and it is supported by a number of publications that treatment status is predictive of utility (i.e., higher utility associated with active treatment compared with BSC).
- 6.54 The ESC noted the EQ-5D-5L scores collected during the CONQUER trial showed no statistically significant difference between treatment arms, while mapped EQ-5D

utility values used in the economic model favour treatment with galcanezumab. The difference between estimated and observed EQ-5D scores was not adequately addressed in the submission.

6.55 The results of the stepped economic analysis, including additional steps calculated during the evaluation, are provided in Table 13 below.

Table 13: Results of the stepped economic evaluation

	Galcanezumab	BSC	Increment
Step 1a: Trial-based analysis, difference in migraine days over 12-weeks, drug costs only			
Costs	\$ [redacted]	\$0	\$ [redacted] ¹
Mean reduction in migraine days	-3.64	-0.65	-2.99
Incremental cost per migraine headache day avoided			\$ [redacted] ¹
Step 1b: Modelled analysis, difference in migraine days in cycle 4 (after 3-month assessment period), drug costs only over 3 cycles (approximately 12 weeks)			
Costs	\$ [redacted]	\$0	\$ [redacted] ¹
Mean reduction in migraine days	-3.7	-0.5	-3.2
Incremental cost per migraine headache day avoided			\$ [redacted] ¹
Step 2a: Difference in migraine days, drug costs over 12 months			
Costs	\$ [redacted]	\$0	\$ [redacted] ¹
Mean migraine headache days	100.5	117.6	17.1
Incremental cost per migraine headache day avoided			\$ [redacted] ¹
Step 2b: Change in migraine days, drug costs, acute treatment and migraine management costs over 12 months			
Costs	\$ [redacted]	\$6,690	\$ [redacted] ¹
Mean migraine headache days	100.5	117.6	17.1
Incremental cost per migraine headache day avoided			\$ [redacted] ¹
Step 3: Utilities applied to health states to generate QALYs; costs over 12 months			
Costs	\$ [redacted]	\$6,690	\$ [redacted] ¹
QALYs	0.710	0.659	0.051
Incremental cost per QALY gained			\$ [redacted] ²
Step 4: QALYs and costs over 5 year time horizon			
Costs	\$ [redacted]	\$28,270	\$ [redacted] ³
QALYs	3.002	2.807	0.195
Incremental cost per QALY gained			\$ [redacted] ⁴

Source: Table 3.8.5 of the submission; additional analyses calculated during the evaluation using Attachment 4.1 Galcanezumab section 3 model

The redacted values correspond to the following ranges:

¹ \$0 to < \$5000

² \$45,000 to < \$55,000

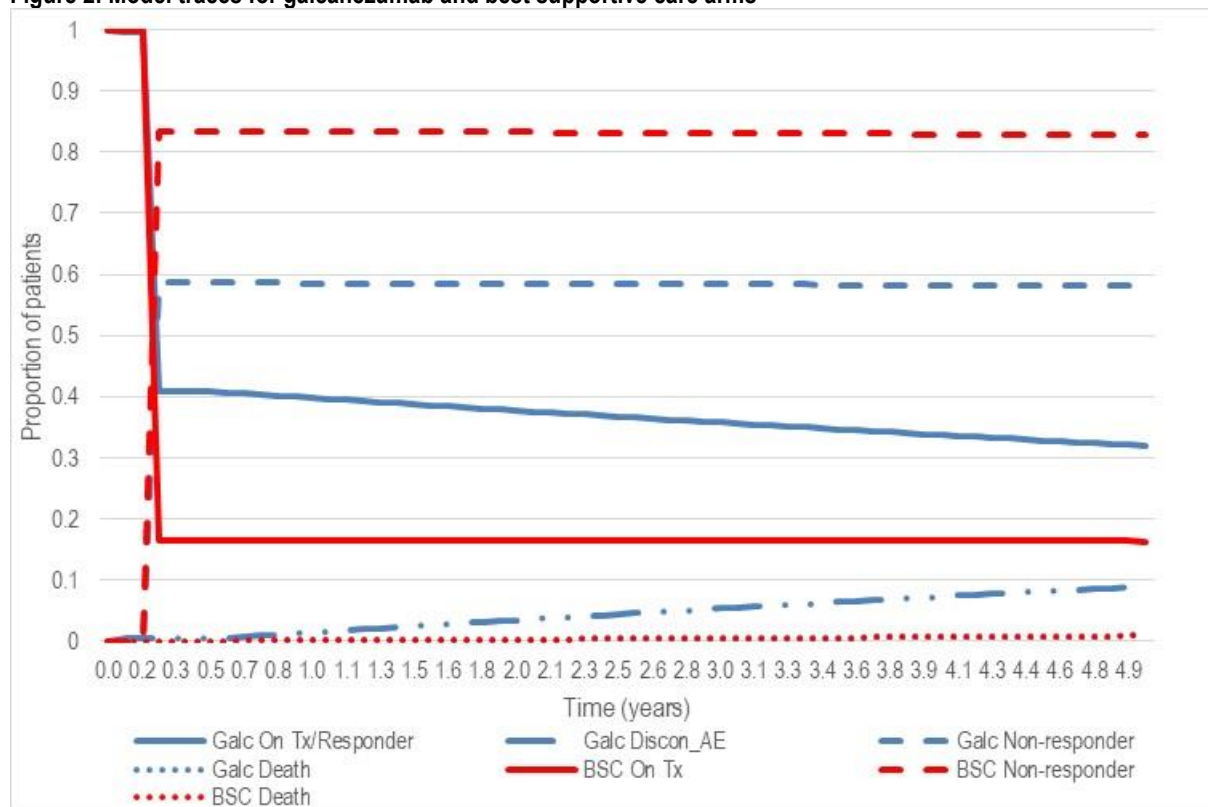
³ \$5,000 to < \$15,000

⁴ \$35,000 to < \$45,000

6.56 Based on the results of the economic model, treatment with galcanezumab was associated with an incremental cost per QALY gained of \$35,000 to < \$45,000, compared to best supportive care (placebo).

6.57 The model trace is summarised in Figure 2 below.

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



Source: Constructed during the evaluation using Attachment 4.1 Galcanezumab Section 3 model
Abbreviations: AE, adverse event; BSC, best supportive care; Galc, galcanezumab; Tx, treatment

- 6.58 The Markov trace shows 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.
- 6.59 The responder health states were associated with lower MHD and greater utility benefit. Responders could only discontinue due to adverse events or death.
- 6.60 The evaluation considered the base case incremental cost effectiveness ratio was unlikely to represent the cost-effectiveness of galcanezumab in clinical practice. There were a number of issues associated with the economic model that limit the reliability of the estimated ICERs:
- Ongoing treatment with galcanezumab was limited to patients who achieved $\geq 50\%$ response, which was associated with very low mean MHDs. Although consistent with the proposed restriction, in practice it is likely that patients with smaller, although still clinically relevant, benefits will continue treatment. 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 ESC noted the structure of the economic model meant that it was difficult to assess different scenarios that explore this risk.

- 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. This also assumes that the response to galcanezumab will be maintained long-term. Current evidence from a long-term open-label trial of galcanezumab, Study CGAJ, did not adequately demonstrate the maintenance of treatment effect, with a majority of responders losing response by month 12. The ESC considered this was a highly optimistic assumption.
- The comparator in the CONQUER trial (placebo) may not be a good proxy for standard of care for the modelled population. In practice, at least a proportion of this population is likely to be using some preventive migraine treatment, which was not allowed in the CONQUER trial. The ESC considered placebo was a reasonable proxy for standard of care (paragraph 6.35).
- The costs and outcomes in the economic model were all based on observed response rates and mean MHDs achieved in the subgroup who had failed treatment with ≥ 3 previous preventive treatments in CONQUER. Patients in this subpopulation appeared to experience relatively severe disease, with an average of approximately 10 monthly MHD at baseline, and a majority of patients (80%) diagnosed with high frequency episodic migraine, defined as 8 to <15 MHD per 30-day period. The ESC considered it was unclear whether disease severity, mean reductions in MHD, and response rates observed in the trial are likely to be similar in the proposed PBS population. Responders achieved very favourable MHD in the model; if there is any change to MHD achieved in clinical practice, the cost effectiveness of galcanezumab will also change.

6.61 Key sensitivity analyses presented in the submission and conducted during the evaluation are summarised in Table 14.

Table 14: Results of key sensitivity analyses

	Incremental cost	Incremental QALYs	ICER
Base case	\$ [redacted]	0.195	\$ [redacted] ¹
Time horizon (base case 5 years)			
1 year	\$ [redacted]	0.0509	\$ [redacted] ²
3 years	\$ [redacted]	0.1321	\$ [redacted] ¹
10 years	\$ [redacted]	0.2984	\$ [redacted] ¹
Proportion of responders (base case response based on the proportion achieving a ≥50% reduction in mean MHD in episodic migraine ≥3 treatment failure subpopulation of CONQUER [41.1%])			
Galcanezumab responders (58.9%) based on BSC arm multiplied by upper 95% CL of estimated RR from OR (3.67)	\$ [redacted]	0.308	\$ [redacted] ³
Galcanezumab responders (25.2%) based on BSC arm multiplied by lower 95% CL of estimated RR from OR (1.53)	\$ [redacted]	0.095	\$ [redacted] ⁴
Proportion of non-responders continuing galcanezumab treatment (base case 0%; responders achieve mean MHD reduction of -6.6; non-responders -1.71)			
10% of non-responders continue treatment; mean MHD for 'on treatment' based on weighted average of responders and non-responders (-5.66)	\$ [redacted]	0.179	\$ [redacted] ¹
20% of non-responders continue treatment; mean MHD for 'on treatment' based on weighted average of responders and non-responders (-5.02)	\$ [redacted]	0.167	\$ [redacted] ²
Reduction in mean MHD associated with treatment (base case mean MHD reduction in responders (GAL -6.60, BSC -6.99) and non-responders (GAL -1.71, BSC 0.83) based on episodic migraine ≥3 treatment failure subpopulation of CONQUER)			
Mean MHD reduction in responders based on upper 95% CL for galcanezumab responders (-4.93) ² ; applied to galcanezumab and BSC arms	\$ [redacted]	0.181	\$ [redacted] ¹
Mean MHD reduction in responders based on lower 95% CL for galcanezumab responders (-8.27) ² ; applied to galcanezumab and BSC arms	\$ [redacted]	0.216	\$ [redacted] ³
Mean MHD reduction in responders based on MCID (-2.0); change in non-responders 0.	\$ [redacted]	0.148	\$ [redacted] ⁴
Duration of treatment effect (base case for duration of model)			
BSC loss of efficacy after 1 year	\$ [redacted]	0.247	\$ [redacted] ³
10% reduction in mean MHD reduction per year for responders	\$ [redacted]	0.184	\$ [redacted] ¹
20% reduction in mean MHD reduction per year for responders	\$ [redacted]	0.174	\$ [redacted] ²
Utility values (base case different utilities per migraine headache day applied to baseline/off treatment, galcanezumab on treatment and BSC on treatment health states)			
Pooled on-treatment utilities	\$ [redacted]	0.126	\$ [redacted] ⁴
Baseline utilities applied to all health states	\$ [redacted]	0.0901	\$ [redacted] ⁵

Source: Table 3.9.2; Attachment 4.1 Galcanezumab Section 3 model

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

¹based on calculation in parameters worksheet of model spreadsheet, corrected to 95% rather than 90% confidence interval

²calculated during the evaluation using a t-distribution, given the small sample size (N=18)

The redacted values correspond to the following ranges

¹ \$35,000 to < \$45,000

² \$45,000 to < \$55,000

³ \$25,000 to < \$35,000

⁴ \$55,000 to < \$65,000

⁵ \$75,000 to < \$85,000

6.62 The results of sensitivity analyses indicate that the model was most sensitive to changes in the assumed utility values, the mean MHD achieved by responders, the proportion of the population continuing treatment, whether the treatment effect was

maintained, and the model duration. Although an analysis where patients who achieved $\geq 30\%$ response were allowed to continue was included in the model, these patients still achieved relatively high MHD reductions and a similar incremental benefit over the BSC arm. The impact of a higher proportion of patients with lower response rates and a lower reduction in mean MHD was unable to be assessed in sensitivity analysis due to the structure of the model, however this represents a likely scenario in clinical practice, particularly if patients in the PBS population do not have the high MHDs observed at baseline in the CONQUER trial and modelled in the submission. 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.

- 6.63 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.

Drug cost/patient/year

- 6.64 The cost of the first 3 months of galcanezumab (prior to response assessment) at the proposed effective DPMQ (including loading dose; applied to 100% of the population) is \$ [REDACTED] (\$ [REDACTED] x 4 scripts).
- 6.65 Assuming 100% treatment compliance for a responder, the cost per patient per year at the proposed effective DPMQ is \$ [REDACTED] (\$ [REDACTED] x 12.166 scripts per annum).
- 6.66 The submission applied the same cost of galcanezumab (4 initial scripts applied to 100% of the population; subsequent costs applied to responders only) in the economic and financial models.

Estimated PBS usage & financial implications

- 6.67 The submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impacts associated with the requested listing.

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Episodic migraine prevalence, diagnosed by physician	Migraine prevalence of 14.6% based on weighted average prevalence of presentations to GP with migraine from small patient survey (Stark 2007). Episodic migraines estimated to be 90% of migraine patients based on reference in erenumab PSD (July 2019) that chronic migraine prevalence is approximately 1.4% of total population, which equates to 10% of Stark (2007) migraine patients. 45.9% of episodic migraine patients were assumed to be diagnosed by a physician based on random sample of patients from a European survey study.	Uncertain: prevalence calculated based on proportion of presentations to general practice that were applied to entire population; and episodic migraine prevalence based on the complement to an approximation of chronic migraine prevalence. Assuming less than half of these patients were diagnosed by a physician reduces the eligible patient pool significantly, and was not reasonable given prevalent migraine patients were estimated based on presentations to general practice, which

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Parameter	Value applied and source	Comment
		implicitly captures the rate of diagnosed patients.
Proportion of patients meeting migraine severity criteria	Vo et al's (2018b) study of users of the Migraine Buddy® smartphone application, of which 27,416 reported migraine headaches during the most recent 28-day period. The submission assumed 10% of these patients were chronic migraine sufferers. 54.9% of the remaining patients reported less than 4 migraine headache days, leaving 45.1% estimated to have experienced 4 to 14 migraine headache days during the most recent 28-day period.	European estimates over a single 28 day period. Assumption that 10% of sample could be classed as chronic migraine. Unclear whether these estimates are applicable to the Australian patient population. Estimate does not incorporate the proportion of these patients with <15 overall headache days.
Proportion of patients who failed ≥3 preventive treatments	Based on proportion of patients (12%) who reported 3 lines of preventive treatment for chronic migraine from Ford (2017), with the submission arguing that the majority of episodic migraine patients would not be eligible for treatment under the proposed PBS restriction.	Based on a small US study. Estimates of the treatment failure population are highly uncertain. The applicability of this estimate to episodic migraine patients who have failed 3 lines of preventive treatment is unclear.
Growth in eligible population	9.39%, based on 10% Medicare Sample analysis, using the mean moving annual growth rate for October 2018-September 2019 for all unique patients with 3 or more treatment lines in a rolling 200 month window.	Growth rate may be higher for the introduction of a therapy with a novel mechanism of action in a treatment failure population. Growth may reflect use in a population that has less severe migraine and may not be cost-effective.
Uptake rate	24% in Year 1 increasing to 48% in Year 6. Assumption based on unpublished sponsor data for CGRP inhibitors, based on burden of illness and lack of alternative treatments	The DUSC considered the annual uptake rates to be uncertain, as it would be unlikely for uptake rates of a novel therapy to be 24% in its first year, particularly when access is restricted by the requirement for a neurologist referral prior to initiation.
Continuing patients at month 3 (responders)	41.1%, based on proportion of patients with ≥50% reduction in migraine headache days during Month 3 in CONQUER (episodic subpopulation with ≥3 prior preventive medication category failures)	A higher rate may be realised in practice. It is likely that patients who achieve less than 50% reduction in migraine headache days may continue treatment which may not represent cost-effective use.
Discontinuations	0.43% in the second and subsequent years of listing, based on the proportion of discontinuations during the double-blind treatment period from the galcanezumab arm of the overall safety population in CONQUER trial.	Trial discontinuations may not be representative of discontinuations in practice, particularly relating to subsequent years of therapy. Inconsistent with approach in Section 3 of submission.
Grandfathered patients	Patients already receiving galcanezumab through an alternative access program may be eligible for PBS subsidised treatment. Approximately 18% of grandfathered patients were considered eligible for the requested listing. The number of patients was based on current numbers of patients, with growth rate applied until 2023 (9.39%), then stabilising with a discontinuation rate applied (0.43%) to year 6.	The submission did not justify why grandfathered patients would be additional to prevalent patients, nor why the eligible grandfathered patient population would continue to grow after a PBS listing for galcanezumab.
MBS costs	Neurologist visits (MBS item 116), first visit, after 3 treatment cycles, then ongoing follow-up every 6 treatment cycles.	Submission stated that assumption of continuing consultations with neurologists (rather than GP) was a likely overestimate.

Source: Table 4.1.1; Table 4.1.2; Table 4.2.3 of the submission.

Abbreviations: PSD, Public Summary Document

6.68 The estimated utilisation and financial impact of a galcanezumab listing for episodic migraine is presented in Table 16 below.

Table 16: Estimated use and financial implications

	2021	2022	2023	2024	2025	2026
Australian population (≥18 years of age)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Migraine prevalence; 14.6%	█ ²	█ ³	█ ³	█ ³	█ ³	█ ³
Patients with EM; 90%	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
EM diagnosed by physician; 45.9%	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
4-14 migraine headache days/month; 45.1%	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁶
Failed ≥3 preventive treatments; 12%	█ ⁷	█ ⁷	█ ⁷	█ ⁸	█ ⁸	█ ⁸
Annual growth in eligible patient population 9.39%	█ ⁸	█ ⁹	█ ⁹	█ ¹⁰	█ ¹¹	█ ¹¹
Uptake rates	24%	32%	36%	40%	44%	48%
Patients initiating treatment (cumulative)	█ ¹²	█ ¹³	█ ¹⁴	█ ¹⁴	█ ¹⁵	█ ¹⁶
New patients per year (estimated by subtracting patients from previous years)	█ ¹²	█ ¹⁷	█ ¹⁷	█ ¹⁷	█ ¹⁷	█ ¹⁷
Continuing patients at month 3; 41.1%	█ ¹⁷	█ ¹⁸	█ ¹⁸	█ ¹⁸	█ ¹⁸	█ ¹⁸
Continuing patients (subsequent years)	█ ¹⁹	█ ¹⁷	█ ¹²	█ ¹²	█ ¹²	█ ¹²
Grandfathered patients	█ ¹⁹	█ ¹⁹	█ ¹⁹	█ ¹⁹	█ ¹⁹	█ ¹⁹
Total scripts dispensed	█ ¹¹	█ ¹¹	█ ²⁰	█ ²⁰	█ ²⁰	█ ²¹
Net cost to PBS/RPBS (less co-payments)	\$█ ²²	\$█ ²³	\$█ ²⁴	\$█ ²⁵	\$█ ²⁶	\$█ ²⁸
Net cost to MBS	\$█ ²⁹	\$█ ²⁹	\$█ ²⁹	\$█ ²⁹	\$█ ²⁹	\$█ ²⁹
Net cost to Government	\$█ ²³	\$█ ²³	\$█ ²⁴	\$█ ²⁵	\$█ ²⁷	\$█ ²⁸

Source: Table 4.2.2; Table 4.2.3; Table 4.2.4; table 4.2.5; Table 4.2.6; Table 4.2.7; Table 4.5.5 of the submission

Abbreviations: EM, episodic migraine

Note: Calculations assume 12.17 scripts/patient/year. Initial treatment (first 3 months) includes 4 scripts, with the remainder of Year 1 including 9.17 scripts per patient.

The redacted values correspond to the following ranges:

¹ > 10,000,000

² 2,000,000 to < 3,000,000

³ 3,000,000 to < 4,000,000

⁴ 1,000,000 to < 2,000,000

⁵ 500,000 to < 600,000

⁶ 600,000 to < 700,000

⁷ 60,000 to < 70,000

⁸ 70,000 to < 80,000

⁹ 80,000 to < 90,000

¹⁰ 90,000 to < 100,000

¹¹ 100,000 to < 200,000

¹² 10,000 to < 20,000

¹³ 20,000 to < 30,000

¹⁴ 30,000 to < 40,000

¹⁵ 40,000 to < 50,000

¹⁶ 50,000 to < 60,000

¹⁷ 5,000 to < 10,000

¹⁸ 500 to < 5,000

¹⁹ <500

²⁰ 200,000 to < 300,000

²¹ 300,000 to < 400,000

²² \$40 million to < \$50 million

²³ \$50 million to < \$60 million

²⁴ \$60 million to < \$70 million

²⁵ \$70 million to < \$80 million

²⁶ \$80 million to < \$90 million

²⁷ \$90 million to < \$100 million

²⁸ \$100 million to < \$200 million

²⁹ \$0 to < \$10 million

- 6.69 The total cost to the PBS/RPBS of listing galcanezumab was estimated to be \$40 million to < \$50million in Year 1, increasing to \$100 million to < \$200 million in Year 6, and a total of \$400 million to < \$500 million in the first 6 years of listing.
- 6.70 Inclusive of costs to the MBS, the total net cost to Government was estimated to be \$50 million to < \$60 million in Year 1, increasing to \$100 million to < \$200 million in Year 6, a cumulative total of \$400 million to \$500 million in the first 6 years of listing.
- 6.71 Overall, the submission estimated that around 2.3% of patients (90% x 45.9% x 45.1% x 12%) with migraine would be eligible for treatment. The projected size of the eligible population was further reduced by the application of an uptake rate (24% to 48%). There is a risk that the population will be larger than the estimate provided in the submission. The submission's estimates were highly uncertain due to a number of issues in estimating uptake and the eligible patient population:
- The prevalence of migraine in Australian adults (14.6%) was based on the proportion of migraine presentations to general practitioners, but were used in the submission to estimate the proportion of the overall population with migraine.
 - The submission assumed that only 45% of potentially eligible episodic migraine patients had physician-diagnosed migraine, based on a random sample of 1680 respondents to a National Health and Wellness Survey from Europe and the UK (Vo 2018a). The DUSC considered it was unclear why the submission had ascertained episodic prevalence estimates from the Vo et al. (2018a) study as it was not applicable. The prevalence was already ascertained based on the BEACH substudy and calculating prevalence estimates again would decrease the size of the eligible pool. The DUSC considered using the prevalence estimates from the Vo et al. (2018a) study would under-estimate the size of the eligible pool.
 - The proportion of patients experiencing 4-14 migraine headache days per month (45.1%) was based on self-reported data from one 28 day period for users of a smartphone application in Europe (Vo 2018b). The DUSC considered estimates derived from this study were uncertain given the short time frame for data collection and the self-reported data, and are of unclear applicability to the Australian patient population. The publication was focussed on a stratified sample of episodic and chronic migraine patients and presented very limited detail on the overall patient population.
 - The submission's estimates of patients who had failed three or more lines of therapy (12%) was based on a chronic migraine population and may not be

applicable to episodic migraine patients. The DUSC considered it was unclear why 12% from the chronic migraine submission was used instead of 14.4% calculated in the submission using the 10% PBS data.

- The annual growth rate in eligible patient numbers (9.39%), based on a 10% PBS sample analysis of migraine-specific treatments, may be higher for the introduction of a therapy with a novel mechanism of action in a treatment failure population. Growth may reflect use in a population with less severe migraine and galcanezumab may not be cost-effective in these patients.
- The proportion of patients continuing with treatment from month 3 for the remainder of year 1 (41.1%) was based on the proportion of patients with a 50% or greater reduction in migraine headache days in month 3 of the CONQUER clinical trial. A higher proportion of patients may continue treatment with galcanezumab in practice. It is likely that some patients who achieve less than a 50% reduction in migraine headache days would continue treatment which may not represent cost-effective use.

6.72 The DUSC noted that 343,286 prescriptions for triptans were dispensed in 2019-20. The DUSC noted that, in the first year of listing, an estimated 100,000 to < 200,000 prescriptions for galcanezumab would be dispensed which suggested that one third of the triptan market would be replaced by galcanezumab. The DUSC considered it would be unlikely for galcanezumab to replace one third of the triptan market upon listing.

6.73 Overall, the DUSC considered:

- The number of eligible patients is likely underestimated as a diagnosed population was used to estimate prevalence but were discounted for diagnosis.
- The high uptake rate is uncertain and the requirement for initiation with a neurologist may reduce uptake.
- There were no offsets for reduced opioid or triptan use, suggesting the therapy is add on. The impact of the listing of galcanezumab on the overall analgesic market should be considered.
- The long term effectiveness and safety of galcanezumab is uncertain.
- In its PSCR, the sponsor reasoned that its analysis of a 10% PBS sample supported its estimate of the utilisation of galcanezumab. However the number of triptan users could not be verified in the sponsor's report, and DUSC considered the sponsor's estimate of 200,000 to < 300,000 migraine medicine users was uncertain.
- The financial estimates were sensitive to a number of parameters affecting the size of the population, particularly migraine prevalence, the proportion of physician diagnosed migraines, and the proportion of continuing patients. Due to

the lack of available data to reliably inform these variables, the estimated financial impacts are associated with considerable uncertainty.

Quality Use of Medicines

- 6.74 The submission described a range of activities to support the quality use of medicines in the treatment of migraine prevention and appropriate use of galcanezumab, including online medical education modules, scientific meetings, and education of clinicians around the treatment paradigm in migraine prevention. The sponsor operates a Product Safety Group in Australia, which is responsible for designated local pharmacovigilance practices in Australia and New Zealand. Activities conducted by the group include receipt and follow-up of adverse event reports, training staff, submission of PSUR, and management of local pharmacovigilance quality systems.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of galcanezumab for the treatment of episodic migraine in patients who have experienced an inadequate response, intolerance, or a contraindication to at least three prophylactic migraine medications. The PBAC considered the magnitude of benefit in this population was uncertain and galcanezumab was not cost-effective at the price requested in the submission. The PBAC considered there is not a clear distinction between treatment-resistant chronic and episodic migraine with patients moving between these diagnoses. The PBAC considered a listing for treatment-resistant migraine would be appropriate and that any resubmission would need to address offsets for patients that might otherwise be attributed for in the chronic migraine population.
- 7.2 The PBAC noted the consumer comments and acknowledged there was a clinical need for additional treatments for people with treatment-resistant migraine.
- 7.3 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. The PBAC noted Migraine Australia was supportive of changing the terminology from episodic and chronic to 'manageable' and 'difficult to manage'.
- 7.4 The PBAC considered best supportive care was an appropriate comparator for patients with episodic migraine who have failed at least three prophylactic migraine medications.
- 7.5 The PBAC noted the submission was based on the CONQUER study, 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 episodic migraine who had received 3 or 4 prior preventative

medications (n=100) which was a subgroup of the ITT population (n=462). The PBAC noted the difference in the change from baseline in the number of migraine headache days per month for galcanezumab vs placebo at 12 weeks was -2.99 (95%CI: -4.53, -1.45). The PBAC considered that treatment with galcanezumab resulted in a modest reduction in the number of migraine headache days compared to placebo.

- 7.6 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.
- 7.7 The PBAC noted the significant issues associated with the economic model (paragraph 6.60) but considered galcanezumab is not cost-effective for episodic migraine at the price requested in the submission. 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.
- 7.8 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. The PBAC considered a proportion of patients with EM included in the financial estimates may already have been captured in the CM submission, noting that patients may cycle between the two definitions.
- 7.9 The PBAC advised any resubmission for episodic migraine should:
- be a major submission;
 - propose a listing for people with treatment-resistant migraine;
 - demonstrate the cost-effectiveness of galcanezumab for the proposed listing; and
 - provide revised financial estimates, accounting for patients that may already have been attributed to the chronic migraine population.
- 7.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected.

8 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.

9 Sponsor's Comment

The sponsor had no comment.