5.03 GALCANEZUMAB, Injection 120 mg in 1 mL single dose pre-filled pen, Emgality®, Eli Lilly Australia Pty Ltd.

1 Purpose of Application

1.1 The submission requested an Authority Required (Streamlined) listing for galcanezumab for treatment of chronic migraine in patients who have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications. This corresponds to the existing PBS restriction for botulinum toxin type A (Botox).

1.2 The submission requested listing on the basis of a cost-minimisation analysis (CMA) compared to Botox. The key components of the clinical issue addressed by the submission are presented in Table 1.

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

Component	Description
Population	Adult patients with treatment-resistant chronic migraine, defined as patients 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 240mg loading dose as the initial dose.
Comparator	Botulinum toxin type A (Botox) 155 U to 195 U administered intramuscularly every 12 weeks.
Outcomes	Reduction in number of migraine headache days, improvement in 50% response rate, reduction in monthly headache days.
Clinical claim	Galcanezumab is non-inferior in terms of efficacy and has comparable safety when compared to Botox.

Source: Table 1.1.1, p14 of the submission.

2 Requested listing

2.1 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					
GALCANEZUMAB 120 mg/1 mL, pre-filled pen	2	2	0	$[redacted] published price $[redacted] effective price	Emgality® Eli Lilly Australia Pty Ltd
GALCANEZUMAB 120 mg/1 mL, pre-filled pen	1	1	1	$[redacted] published price $[redacted] effective price	
Continuing					
GALCANEZUMAB 120 mg/1 mL, pre-filled pen	1	1	5	$[redacted] published price $[redacted] effective price	

Category/Program:	General Schedule - Section 85
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Chronic migraine
Treatment phase:	Initial - *loading dose*
Restriction: General Schedule	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	Must be treated by a neurologist
Clinical criteria:	Patient must have experienced an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months, prior to commencement of treatment with *this drug for this condition* ~~galcanezumab~~ AND Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with *this drug for this condition* ~~galcanezumab~~ AND *The treatment must not be in combination with botulinum toxin* AND Patient must be appropriately managed ~~by his or her practitioner~~ for medication overuse headache, prior to initiation of treatment with *this drug* ~~galcanezumab~~
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.
Administrative advice:	~~This drug is not PBS-subsidised for use in combination with botulinum toxin type A~~

Episodicity:	Chronic
Severity:	N/A
Condition:	Migraine
PBS Indication:	Chronic ~~M~~migraine
Treatment phase:	Initial ~~– Balance of supply~~
Restriction:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	Must be treated by a neurologist.

Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must have experienced an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months, prior to commencement of t*reatment with this medicine* ~~galcanezumab~~. AND Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of *treatment with this medicine* ~~galcanezumab~~. AND Patient must continue to be appropriately managed ~~by his or her practitioner~~ for medication overuse headache, prior to initiation of treatment with this medicine ~~galcanezumab~~. AND *The treatment must not be in combination with botulinum toxin* ~~AND~~ ~~Patient must not receive more than 3 months of treatment under this restriction~~.
Population criteria:	~~Patient must be aged 18 years or older.~~
Foreword	N/A
Definitions	N/A
Prescriber Instructions	Prophylactic migraine medications are propranolol, amitriptyline, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate or topiramate.
Administrative Advice	~~This drug is not PBS-subsidised for use in combination with botulinum toxin type A.~~

Treatment phase:	Continuing
Treatment criteria:	Must be treated by a neurologist
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine headache days per month ~~after three treatment cycles (3 months)~~ in order to be eligible for continuing PBS-subsidised treatment AND *The treatment must not be in combination with botulinum toxin* AND Patient must *continue* be appropriately managed ~~by his or her practitioner~~ for medication overuse headache~~, prior to initiation of treatment with galcanezumab~~

Source: Table 1.4.2 to Table 1.4.4, p27-29 of the submission.

2.2 The PBAC noted the requested restriction was consistent with the PBS listing of Botox for chronic migraine, although with the following differences:

- For continuing treatment, the requested restriction specifies a 50% or greater reduction in 'migraine headache days' after 3 months while the Botox restriction uses the terminology 'headache days' after 24 weeks (6 months).
- An assessment timepoint for continuing treatment of 3 months, instead of the 24 weeks (6 months) in the Botox restriction.

- The list of prophylactic medicines differed from those included in the Botox criteria. The PBAC considered the proposed list was appropriate and consistent with local treatment guidelines for chronic migraine. The PBAC noted the Botox restriction should be updated for consistency.

2.3 The subgroup from REGAIN selected to represent the PBS population included patients who had failed ≥3 prior medications but these patients could only have failed 1 or 2 classes of medications (as the trial excluded patients who had failed ≥3 classes of medications). While the subgroup from REGAIN may not fully represent the PBS population, the PBAC noted the clinical claim in the submission was supported in the ITT, mITT subgroup and the treatment-failure subgroup populations.

2.4 The limited evidence on the natural history of chronic migraine suggests that remission may occur[1] and the PBAC noted the proposed restriction provided ongoing continuing treatment, with no requirement for a trial of treatment withdrawal.

2.5 The PBAC considered it was appropriate to restrict access to galcanezumab to patients over the age of 18 years of age as proposed in the submission and consistent with the TGA approved indication (see paragraph 3.1).

2.6 The PBAC noted the proposed criteria required patients to be treated by neurologists for both the initial and continuing restrictions. This was appropriate for the initial criteria but the PBAC considered it would be appropriate to allow continuing prescriptions to be written by or in consultation with a neurologist.

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

3 Background

Registration status

3.1 Galcanezumab was approved by the TGA on the 22 May 2019 for the "prophylaxis of migraine in adults".

3.2 The ESC noted the TGA indication (migraine) is much broader than the proposed PBS restriction (chronic migraine in patients who have inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications) and considered galcanezumab may be used outside the proposed PBS restriction criteria. The PBAC agreed with the ESC and considered inclusion of galcanezumab in the Botox risk sharing agreement was necessary to address this risk.

[1] Manack, A., Buse, D. C., Serrano, D., Turkel, C. C. & Lipton, R. B. Rates, predictors, and consequences of remission from chronic migraine to episodic migraine. *Neurology* 76, 711–718 (2011)

Previous PBAC consideration

3.3 This was the first submission to the PBAC for galcanezumab for the treatment of chronic migraine. There have been two submissions to the PBAC for erenumab for use in chronic migraine, in July 2018 and March 2019; and four submissions for Botox for use in chronic migraine, in November 2011, July 2012, July 2013 and March 2018.

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

4 Population and disease

4.1 Migraine is a form of headache that is defined as a recurrent headache with a pulsating quality, unilateral location, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

4.2 Migraine is characterised by recurrent headache, lasting 4 to 72 hours and often accompanied by symptoms such as nausea, vomiting and hypersensitivity to light and sound. The target population for treatment with galcanezumab are adult patients with chronic migraine, defined as 15 or more headache days per month, at least 8 of which have to be typical migraine days.

4.3 Of patients with chronic migraine, the specified treatment population for galcanezumab is patients who have failed ≥3 prophylactic medications, which corresponds with the treatment population for Botox.

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

5 Comparator

5.1 The submission nominated Botox as the main comparator as it is the only PBS-listed treatment for the same population as sought for galcanezumab, patients who have not responded, were intolerant or had contraindications to at least 3 prophylactic migraine medications. The ESC considered the selection of Botox as the main comparator was appropriate, although best supportive care (BSC) could also be considered an appropriate comparator. The ESC noted that while galcanezumab cannot be used with Botox, it may be used before or after Botox (i.e., used sequentially) in a proportion of patients. The ESC also considered other migraine preventative treatments may be considered comparators if galcanezumab is used earlier in the treatment algorithm, consistent with how it was used in the clinical trial.

5.2 The submission identified erenumab as a supplementary, near-market comparator and an indirect comparison of galcanezumab and erenumab was provided. The inclusion of erenumab as a near-market comparator in the submission was appropriate; however, the PBAC noted erenumab was rejected the March 2019 PBAC meeting and was not considered at the July 2019 PBAC meeting.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the clinical trial data (in particular the relevance of the high placebo response observed), clarified the place of galcanezumab in clinical practice and addressed other questions raised by the Committee. The clinician considered that if a patient was well controlled on galcanezumab, the period between injections may be extended but it was likely migraines would return if treatment was stopped entirely.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (56), health care professionals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described the debilitating physical, mental and social impact of chronic migraine and the range of potential benefits of treatment with galcanezumab and the other CGRP inhibitors. 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. 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. Many patients expressed their concern at being able to afford the medicine if it was not listed on the PBS.

6.3 The PBAC noted the advice received from Headache Australia that while there are numerous treatments available for the prevention of migraine, there is a clinical need for better medications with fewer side effects.

Clinical trials

6.4 The submission was based on an indirect comparison using one galcanezumab trial (REGAIN; N=836) and two Botox trials (PREEMPT 1 and PREEMPT 2; N=1,384), with placebo as the common comparator. The Botox trials have previously been considered by the PBAC in its consideration of erenumab in July 2018 and March 2019 and in its consideration of Botox in November 2011, July 2012, July 2013 and March 2018.

6.5 The submission included an indirect comparison versus erenumab, which utilised Study 295 for erenumab. Study 295 has been previously considered by the PBAC as part of the July 2018 and March 2019 PBAC submissions for erenumab.

6.6 The indirect comparisons were based on post-hoc subgroups selected to correspond to the requested PBS restriction, patients who had failed ≥3 prophylactic medications.

For galcanezumab, this subgroup comprised 13% of the REGAIN trial intention to treat (ITT) population. For Botox this comprised 35% of the PREEMPT ITT populations and for erenumab, this comprised 35% of the Study 295 ITT population.

6.7 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Galcanezumab		
REGAIN	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Chronic Migraine – the REGAIN Study: Final Results from the Double-Blind Treatment Phase and Interim Results from the Open-Label Treatment Phase A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 in Patients with Chronic Migraine – the REGAIN Study: Final Results from the Open-Label Treatment and Post-Treatment Phases Detke HC, Goadsby PJ, Wang S, Friedman DI et al. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study.	Eli Lilly Clinical Study Report 18 September 2017 Eli Lilly Clinical Study Report 5 February 2019 Neurology 2018 91(24): e2211-e2221.
CGAJ	A Phase 3, Long-Term, Open-Label Safety Study of LY2951742 in Patients with Migraine: Results from the Open-Label Treatment Phase Camporeale AD, Kudrow R, Sides S, Wang A, et al. A phase 3, long-term, open-label safety study of galcanezumab in patients with migraine.	Eli Lilly Clinical Study Report 13 September 2017 BMC Neurol 2018; 18(1): 188. doi: 10.1186/s12883-018-1193-2.
Botox		
PREEMPT I	Aurora SK et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial.	Cephalalgia 2010; 30(7): 793-803.
PREEMPT 2	Diener HC et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial.	Cephalalgia 2010; 30(7): 804-814.
PREEMPT 1 and PREEMPT 2 pooled analysis	Dodick DW et al. OnabotulinumtoxinA for treatment of chronic migraine: Pooled results from the double-blind, randomized, placebo-controlled phase of the PREEMPT clinical program. Aurora SK et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program.	Headache 2010; 50(6): 921-936. Headache 2011; 51(9): 1358-1373.
Erenumab		
Study 295	Tepper S Ashina M, Reuter U, Brandes JL et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Ashina MS, Tepper JL, Brandes U, Reuter G et al. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study.	Lancet Neurol 2017; 16: 425-434. Cephalalgia 2018; 38(10): 1611-1621.

Source: Table 2.2.1, p38-39; Table 1.1.1, p5 Attachment 4.6 of the submission.

6.8 The key features of the randomised trials included in the indirect comparisons versus Botox and erenumab are provided in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Galcanezumab vs. placebo					
REGAIN	ITT=836 mITT[a]=604 subgrp= 104	R, DB, MC 12 weeks	Low (High for subgrp)	ITT; mITT[a]; subgroup (failed ≥3 prophylactic medications)	Change from baseline in monthly migraine headache days
Botox vs. placebo					
PREEMPT 1 and PREEMPT 2 pooled analysis	ITT=1,384 subgrp= 479	R, DB, MC 24 weeks	Low (High for subgrp)	ITT and subgroup (failed ≥3 prophylactic medications)	Change from baseline in headache days
Erenumab vs. placebo					
Study 295	ITT=468 or 469[b] subgrp=163 or 167[b]	R, DB, MC 12 weeks	Low (High for subgrp)	ITT and subgroup (failed ≥3 prophylactic medications)	Change from baseline in monthly migraine days

[a] The mITT population consisted of patients for whom migraine headache days were defined as ≥4 hours (corresponding to the PREEMPT and erenumab trials) instead of ≥30 minutes as used in the REGAIN ITT population, or when a patient took acute medication on the corresponding day. Statistical analyses used ANCOVA to correspond to the methodology used in the PREEMPT trials instead of the mixed model repeated measures used in REGAIN for the ITT population comparisons.

[b] The size of the population varied depending on the outcome assessed.

DB=double blind; ITT=intention-to-treat; MC=multi-centre; mITT=modified ITT; R=randomised; subgrp=subgroup

Source: Compiled from Section 2 and Attachment 4.6 of the submission

6.9 The submission identified a modified ITT population (mITT) which was a subgroup of the ITT population. The submission stated that given the differences in the definition of migraine and headache used by the REGAIN and PREEMPT trials, a post-hoc analysis of the REGAIN individual patient data was conducted to ensure that the definition of endpoints and methods of statistical analysis used in REGAIN corresponded to those used in the PREEMPT trials.

6.10 In REGAIN, a migraine headache day was defined as a calendar day with a headache lasting ≥30 minutes with features meeting ICHD-3 criteria for migraine or probable migraine. A headache also qualified as a migraine if the patient believed it was a migraine at onset and was relieved by a triptan or ergot. In the PREEMPT trials, a migraine day was defined as a calendar day with ≥4 continuous hours of headache meeting ICHD-2 criteria for migraine. The key difference for the REGAIN trial was the specified duration of ≥30 minutes, compared to the headache duration of ≥4 hours specified in the PREEMPT trials. Additionally, the REGAIN trial used mixed model repeated measures to analyse change from baseline data, while the PREEMPT trials used ANCOVA.

6.11 As well as the alteration of headache duration to ≥4 hours, the submission included the criterion of 'or when a patient took acute medication on the corresponding day' as part of the defining criteria for the mITT population.

6.12 The mITT subgroup from REGAIN was used by the submission for the indirect comparison versus Botox, and was also the population from which the treatment failure subgroup was identified. This latter subgroup was identified by the submission to meet the requested PBS restriction for galcanezumab, specifically patients with ≥3 prior preventive migraine treatment failures due to efficacy or safety/tolerability issues.

6.13 The patient demographic and baseline disease characteristics were similar between the REGAIN and PREEMPT ITT populations, although no information was available on these characteristics for the PREEMPT subgroup population. There was a considerable difference in placebo responses across the ITT, mITT and treatment failure subgroup of REGAIN, and the ITT and treatment failure subgroup of the PREEMPT studies (see table below). The difference in placebo response suggested a lack of transitivity in that comparison.

Table 4: Responses in the placebo arms of REGAIN and the PREEMPT trials

Outcome	REGAIN – placebo			PREEMPT 1 and 2 - placebo	
	ITT	mITT	Subgroup	ITT	Subgroup
Change from baseline migraine headache days	-2.74 days	[redacted] days	[redacted] days	-6.26 days	-4.28 days
≥50% reduction in migraine headache days	24.7%	NR	NR	36.4%	NR

ITT=intention-to-treat; mITT=modified intention-to-treat; NR=not reported
Source: Table 2.5.1, p63; Table 2.6.5, p94; Table 2.6.11, p100 of the submission.

6.14 For the galcanezumab and erenumab indirect comparison, the ITT populations had similar patient demographic characteristics, although there were some differences in baseline disease characteristics.

6.15 Overall, the PBAC considered there were differences between the trials that may impact on the transitivity assumption of the indirect comparisons for galcanezumab versus Botox and versus erenumab (i.e., differences in outcome definitions, patient demographics, placebo response, size of subgroups).

Comparative effectiveness

Indirect comparison: galcanezumab versus Botox

6.16 The submission specified a non-inferiority margin based on previous acceptance by the PBAC that a reduction of 2 to 3 headache days per month could be considered to be a clinically important benefit (July 2012 Botox PSD), using the upper 95% confidence interval for mean differences for change in headache days.

6.17 Results for the indirect comparisons of galcanezumab and Botox for change from baseline in migraine headache days are provided below.

Table 5: Results across all groups for change from baseline in migraine headache days – galcanezumab vs. Botox

Trial	Mean change from baseline (SE or 95% CI) in migraine headache days			Mean difference (95% CI)
	Galcanezumab	Placebo	Botox	
ITT population[a]				
REGAIN (12 weeks)	N=273 -4.83 (0.44)	N=538 -2.74 (0.36)	-	**-2.09 (-2.92, -1.26)**
Pooled PREEMPT trials (24 weeks)	-	N=696 -6.2 (-6.69, -5.68)	N=688 -8.2 (-8.69, -7.70)	**-2.00 (-2.67, -1.27)**
			Indirect comparison	-0.09 (-1.18, 1.0)
Identified subgroup (≥3 treatment failures; sourced from ITT population for REGAIN)				
REGAIN (12 weeks)	N=[redacted] [redacted] ([redacted])	N=[redacted] [redacted] ([redacted])		[redacted] ([redacted], [redacted])
Pooled PREEMPT trials (24 weeks)		N=248 -4.28 (0.41)	N=231 -7.12 (0.44)	**-2.88 (-4.24, -1.51)**
			Indirect comparison	[redacted] ([redacted], [redacted])
Modified ITT population (mITT; migraine definition changed to ≥4 hours from ≥30 minutes in ITT population[b]**)**				
REGAIN (12 weeks)	N=[redacted] [redacted] ([redacted])	N=[redacted] [redacted] ([redacted])	-	[redacted] ([redacted], [redacted])
Pooled PREEMPT trials (24 weeks)	-	N=696 -6.26 (0.26)	N=688 -8.21 (0.25)	**-1.96 (-2.66, -1.25)**[c]
			Indirect comparison	[redacted] ([redacted], [redacted])
Identified subgroup (≥3 treatment failures; sourced from mITT population for REGAIN)				
REGAIN (12 weeks)	N=[redacted] [redacted] ([redacted])	N=[redacted] [redacted] ([redacted])	-	[redacted] ([redacted], [redacted])
Pooled PREEMPT trials (24 weeks)	-	N=248 -4.28 (0.41)	N=231 -7.12 (0.44)	**-2.88 (-4.24, -1.51)**
			Indirect comparison	[redacted] ([redacted], [redacted])

[a] The ITT population that was assessed in REGAIN (N=811) was based on patients with non-missing change from baseline in migraine headache days data, which was less than the overall ITT population (N=836).

[b] The mITT population consisted of patients for whom migraine headache days were defined as ≥4 hours instead of ≥30 minutes as used in the REGAIN ITT population, or when a patient took acute medication on the corresponding day. Statistical analyses used ANCOVA to correspond to the methodology used in the PREEMPT trials instead of the mixed model repeated measures used in REGAIN for the ITT population comparisons.

[c] The Botox – placebo differences reported here were based on a meta-analysis conducted by the submission instead of the values reported in the PREEMPT trial publications.

CI=confidence interval; NR=not reported; SE=standard error **bold**=statistically significant

Source: Table 2.5.1, p63; Table 2.5.7, p73; Table 2.6.8, p98; Table 2.6.12, p101 of the submission. Subgroup data from the ITT population was provided in the PSCR.

6.18 Within each trial the reduction in migraine headache days was statistically significant for the active treatment, galcanezumab or Botox, compared to placebo across the ITT population, mITT subgroup and treatment failure subgroups. The indirect comparisons using the ITT, the mITT subgroup and the treatment failure subgroups showed no statistically significant differences between galcanezumab and Botox. The submission stated that as the upper confidence intervals for the difference in change in headache days did not cross the PBAC-accepted clinically meaningful reduction of 2 to 3 days, a claim of non-inferiority of galcanezumab and Botox was supported. The PBAC noted the larger incremental benefit of galcanezumab versus placebo and versus Botox when the analyses were based on the post-hoc subgroups but considered these analyses to be less reliable than the analyses based on the ITT and mITT population.

The PBAC also noted that much of the incremental benefit was driven by a lower placebo response in the galcanezumab studies than in the Botox studies.

6.19 The table below provides the results of the indirect comparison of galcanezumab and Botox for change from baseline in headache days.

Table 6: Results across all groups for change from baseline in headache days - galcanezumab vs. Botox

Trial	Mean change from baseline (SE or 95% CI) in headache days			Mean difference (95% CI)
	Galcanezumab	Placebo	Botox	
ITT population				
REGAIN (12 weeks)	N=273 -4.84 (0.43)	N=538 -3.01 (0.35)	-	**-1.84 (-2.65, -1.02)**
Pooled PREEMPT trials (24 weeks)	-	N=696 -6.6 (-7.07, -6.08)	N=688 -8.4 (-8.90, -7.92)	**-1.8 (-2.52, -1.13)**
			Indirect comparison	-0.04 (-1.11, 1.03)
Identified subgroup (≥3 treatment failures; sourced from ITT population for REGAIN)				
REGAIN (12 weeks)	N=[redacted] [redacted] ([redacted])	N=[redacted] [redacted] ([redacted])	-	**[redacted] (-[redacted], [redacted])**
Pooled PREEMPT trials (24 weeks)	-	N=248 -4.68 (0.41)	N=231 -7.37 (0.44)	**-2.72 (-4.19 -1.26)**
			Indirect comparison	[redacted] ([redacted], [redacted])
Modified ITT population (mITT; migraine definition changed to ≥4 hours from ≥30 minutes in ITT population[b])				
REGAIN (12 weeks)	N=[redacted] [redacted] ([redacted])	N=[redacted] [redacted] ([redacted])	-	**[redacted] ([redacted], [redacted])**
Pooled PREEMPT trials (24 weeks)	-	N=696 -6.66 (0.25)	N=688 -8.51 (0.25)	**-1.86 (-2.74, -0.97)[c]**
			Indirect comparison 12 weeks REGAIN vs. 24 weeks PREEMPT	[redacted] ([redacted], [redacted])
Identified subgroup (≥3 treatment failures; sourced from mITT population for REGAIN)				
REGAIN (12 weeks)	N=[redacted] [redacted] ([redacted])	N=[redacted] [redacted] ([redacted])	-	**[redacted] ([redacted], [redacted])**
Pooled PREEMPT trials (24 weeks)	-	N=248 -4.68 (0.41)	N=231 -7.37 (0.44)	**-2.72 (-4.19 -1.26)**
			Indirect comparison	[redacted] ([redacted], [redacted])

[a] The ITT population that was assessed in REGAIN (N=811) was based on patients with non-missing change from baseline in migraine headache days data, which was less than the overall ITT population (N=836).

[b] The mITT population consisted of patients for whom migraine headache days were defined as ≥4 hours instead of ≥30 minutes as used in the REGAIN ITT population, or when a patient took acute medication on the corresponding day. Statistical analyses used ANCOVA to correspond to the methodology used in the PREEMPT trials instead of the mixed model repeated measures used in REGAIN for the ITT population comparisons.

CI=confidence interval; NR=not reported; SE=standard error **bold**=statistically significant

Source: Table 2.5.3, p67; Table 2.5.6, p72; Table 2.6.9, p98; Table 2.6.10, p99 of the submission. Subgroup data from the ITT population was provided in the PSCR.

6.20 The indirect comparisons showed there were no statistically significant differences between galcanezumab and Botox for change from baseline in headache days for the ITT, mITT subgroup and treatment failure subgroup populations.

6.21 The table below provides the results of the indirect comparison of galcanezumab and Botox for the outcome of ≥50% reduction in migraine headache days. This comparison was undertaken using only the ITT populations as subgroup data for this outcome was not available for the PREEMPT trials.

Table 7: Indirect comparison of galcanezumab and Botox for ≥50% reduction in migraine headache days

Trial	≥50% reduction in monthly migraine headache days n with event/N (%)			OR (95% CI)
	Galcanezumab	Placebo	Botox	
ITT population				
REGAIN (12 weeks)	90/256 (35.2%)	123/498 (24.7%)	-	**1.65 (1.19, 2.29)**
Pooled PREEMPT trials (24 weeks)	-	202/555 (36.4%)	260/539 (48.2%)	**1.62 (1.19, 2.21)[a]**
			Indirect comparison	1.02 (0.65, 1.6)

[a] The Botox – placebo differences reported here were based on a meta-analysis conducted by the submission instead of the values reported in the PREEMPT trial publications.

CI=confidence interval; OR=odds ratio; **bold**=statistically significant

Source: Table 2.6.11, p100 of the submission.

6.22 The indirect comparison showed no statistically significant difference between galcanezumab and Botox for proportion of patients with ≥50% reduction in migraine headache days.

Indirect comparison: galcanezumab versus erenumab

6.23 The tables below provide the results of the indirect comparison of galcanezumab and erenumab for change from baseline in migraine headache days and the proportion of patients with ≥50% reduction in migraine headache days in the ITT and the treatment failure subgroup populations.

Table 8: Indirect comparison of galcanezumab and erenumab – ITT population

Trial	Mean change from baseline (SE) in migraine headache days			Mean difference (95% CI)
	Galcanezumab	Placebo	Erenumab	
REGAIN (over 12 weeks)	N=273 -4.8 (0.4)	N=538 -2.7 (0.4)	-	**-2.1 (-3.21, -0.99)**
Study 295 (70 mg) (at 12 weeks)	-	N=281 -4.2 (0.4)	N=188 -6.6 (0.4)	**-2.4 (-3.51, -1.29)**
Indirect comparison galcanezumab vs. erenumab 70 mg				0.3 (-1.27, 1.87)
Study 295 (140 mg) (at 12 weeks)	-	N=281 -4.2 (0.4)	N=187 -6.6 (0.4)	**-2.4 (-3.51, -1.29)**
Indirect comparison galcanezumab vs. erenumab 140mg				0.3 (-1.27, 1.87)
	≥50% reduction in migraine headache days n with event/N (%)			**Treatment effect OR (95% CI)**
	Galcanezumab	**Placebo**	**Erenumab**	
REGAIN (over 12 weeks)	75/273 (27.5%)	83/538 (15.4%)	-	**2.08 (1.46, 2.96)**
Study 295 (70 mg) (at 12 weeks)	-	66/281 (23.5%)	75/188 (39.9%)	**2.16 (1.45, 3.23)**
Indirect comparison galcanezumab vs. erenumab 70 mg				0.96 (0.56, 1.64)
Study 295 (140 mg) (at 12 weeks)		66/281 (23.5%)	77/187 (41.2%)	**2.28 (1.53, 3.41)**
Indirect comparison galcanezumab vs. erenumab 140 mg				0.91 (0.53, 1.55)

CI=confidence interval; OR=odds ratio; SE=standard error **bold**=statistically significant

Source: Tables 1.4.3-1.4.6, p23-25 of Attachment 4.6 of the submission.

Table 9: Indirect comparison of galcanezumab and erenumab – treatment failure subgroup

Trial	Mean change from baseline (SE) in migraine headache days			Mean difference (95% CI)
	Galcanezumab	Placebo	Erenumab	
REGAIN (over 12 weeks)	N=36 -5.6 (1.0)	N=102 -0.4 (0.8)	-	**-5.3 (-7.67, -2.83)**
Study 295 (70 mg) (at 12 weeks)	-	NR	N=NR -2.5 (0.9)	**-2.5 (-4.25, -0.75)**
Indirect comparison galcanezumab vs. erenumab 70 mg				-2.8 (-5.73, 0.23)
Study 295 (140 mg) (at 12 weeks)	-	NR	N=NR -4.1 (0.9)	**-4.1 (-5.85, -2.35)**
Indirect comparison galcanezumab vs. erenumab 140 mg				-1.2 (-4.13, 1.83)
	≥50% reduction in migraine headache days n with event/N (%)			**Treatment effect OR (95% CI)**
	Galcanezumab	**Placebo**	**Erenumab**	
REGAIN (over 12 weeks)	11/36 (30.6%)	7/102 (6.9%)	-	**5.97 (2.10, 16.98)**
Study 295 (70 mg) (at 12 weeks)	-	15/98 (15.3%)	23/69 (33.3%)	**2.77 (1.32, 5.82)**
Indirect comparison galcanezumab vs. erenumab 70 mg				2.16 (0.60, 7.78)
Study 295 (140 mg) (at 12 weeks)		15/98 (15.3%)	25/65 (38.5%)	**3.46 (1.65, 7.27)**
Indirect comparison galcanezumab vs. erenumab 140 mg				1.73 (0.48, 6.22)

CI=confidence interval; NR=not reported; OR=odds ratio; SE=standard error **bold**=statistically significant
Source: Tables 1.4.11-1.4.14, p29-31 of Attachment 4.6 of the submission.

6.24 The indirect comparisons showed no statistically significant differences between galcanezumab and erenumab for change from baseline in migraine headache days and proportion of patients with ≥50% reduction in migraine headache days across both the ITT and treatment failure populations.

Comparative harms

Galcanezumab and Botox – safety outcomes

6.25 The submission provided safety results for the overall (ITT) trial populations of REGAIN and the PREEMPT trials as well as safety results for the treatment failure subgroup in REGAIN. The table below provides a summary of adverse events (AEs) across the REGAIN and PREEMPT trials.

Table 10: Summary of adverse events in REGAIN and PREEMPT 1 and PREEMPT 2

Adverse event	REGAIN		PREEMPT 1 and 2	
	Galcanezumab (N=273)	Placebo (N=558)	Botox (N=687)	Placebo (N=692)
AEs	159 (58.2%)[a]	279 (50.0%)	429 (62.4%)	358 (51.7%)
Treatment-related AEs	[redacted]	[redacted]	202 (29.4%)	88 (12.7%)
Injection site pain	16 (5.9%)	24 (4.3%)	22 (3.2%)	14 (2.0%)
Injection site reaction	8 (2.9%)	10 (1.8%)	NR	NR
Injection site erythema	4 (1.5%)	5 (0.9%)	NR	NR
Headache	[redacted]	[redacted]	20 (2.9%)	11 (1.6%)
Neck pain	[redacted][a]	[redacted]	46 (6.7%)	15 (2.2%)
Nausea	[redacted]	[redacted]	NR	NR
Dizziness	[redacted]	[redacted]	NR	NR
Muscular weakness	[redacted]	[redacted]	38 (5.5%)	2 (0.3%)
Musculoskeletal pain	[redacted]	[redacted]	15 (2.2%)	5 (0.7%)
Musculoskeletal stiffness	[redacted]	[redacted]	16 (2.3%)	5 (0.7%)
Eyelid ptosis	[redacted]	[redacted]	23 (3.3%)	2 (0.3%)
Myalgia	[redacted]	[redacted]	18 (2.6%)	2 (0.3%)
SAEs	1 (0.4%)	4 (0.7%)	33 (4.8%)	16 (2.3%)
Patients with ≥1 SAE	1 (0.4%)	4 (0.7%)	33 (4.8%)	16 (2.3%)
Treatment-related SAEs	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Discontinuation due to AEs	1 (0.4%)	6 (1.1%)	26 (3.8%)	8 (1.2%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[a] Significantly different from placebo; p<0.05

AE=adverse events; NR=not reported; SAE=serious adverse events

Source: Table 2.5.11, p78; Table 2.5.13, p80; and Table 2.5.14, p81 of the submission.

6.26 Botox had a higher incidence of AEs, treatment-related AEs, serious AEs (SAEs) and discontinuation related to AEs in the pooled PREEMPT trials compared to galcanezumab-treated patients in REGAIN.

6.27 The PBAC noted the incidence of injection site pain was higher in the galcanezumab treatment arm (5.9%) in REGAIN compared to the Botox treatment arm (3.2%) in the pooled PREEMPT trials although the difference between active treatment and placebo for the AE of injection site pain was similar for the REGAIN and PREEMPT studies (1.6% and 1.2%, respectively).

6.28 In the treatment failure subgroup there were numerically higher incidences of AEs (73.1%) and treatment-related AEs ([redacted]) in the galcanezumab group compared to the placebo group (48.2% and [redacted]%, respectively). The incidence of overall AEs and treatment-related AEs in the subgroup was higher than that observed in the ITT population.

6.29 The PBAC noted the REGAIN trial excluded patients with recent cardiovascular events and that there is a theoretical cardiovascular risk associated with CGRP inhibitors. The PBAC noted the proposed TGA Risk Management Plan included pharmacovigilance measures to address the risks associated with patients at high risk of cardiovascular and cerebrovascular events, including in patients ≥ 65 years; hypertension during pregnancy; use in pregnancy; and long-term safety (including malignancy). The PBAC also noted there is substantially more, longer-term safety data available for Botox in

a broader patient population (i.e., use in migraine in a wider cross section of the population and across indications other than migraine).

Galcanezumab and erenumab – safety outcomes

6.30 The table below provides a summary of the safety outcomes provided for galcanezumab and erenumab.

Table 11: Summary of adverse events in REGAIN and Study 295 (erenumab)

	REGAIN		Study 295		
	Galcanezumab (N=273)	Placebo (N=558[a])	Erenumab 70 mg (N=190)	Erenumab 140 mg (N=188)	Placebo (N=282)
AEs	159 (58.2%)[b]	279 (50.0%)	83 (43.7%)	88 (46.8%)	110 (39.0%)
Treatment-related AEs	63 (23.1%)	102 (18.3%)	NR	NR	NR
SAEs	1 (0.4%)	4 (0.7%)	6 (3.2%)	2 (1.1%)	7 (2.5%)
Treatment-related SAEs	0 (0.0%)	0 (0.0%)	NR	NR	NR
Discontinuation due to AEs	1 (0.4%)	6 (1.1%)	0 (0.0%)	2 (1.1%)	2 (0.7%)
Deaths	0 (0.0%)	0 (0.0%)	NR	NR	NR
Treatment-emergent AEs[c]					
Nasopharyngitis	17 (6.2%)	26 (4.7%)	6 (3.2%)	3 (1.6%)	16 (5.7%)
Injection site pain	17 (6.2%)	24 (4.3%)	7 (3.7%)	7 (3.7%)	3 (1.1%)
URTI	9 (3.3%)	13 (2.3%)	5 (2.6%)	6 (3.2%)	4 (1.4%)
Migraine	[redacted]	[redacted]	3 (1.6%)	5 (2.7%)	3 (1.1%)

[a] Tables 1.5.2 and 1.5.3 of Attachment 4.6 of the submission reported the N for the REGAIN placebo group as N=557. However that value did not concur with the CSR tables cited as the source of value, nor did it concur with the placebo N in the CSR for safety outcomes. Hence the value was altered to N=558, which also corresponds to the N presented by the submission for safety outcomes in the galcanezumab versus Botox comparison.

[b] Significantly different from placebo; p<0.05

[c] Only the treatment-emergent AEs which had data available for both galcanezumab and erenumab are presented above. The submission included additional treatment-emergent AEs which were reported for one trial only.

AE=adverse events; NR=not reported; SAE=serious adverse events; URTI=upper respiratory tract infection

Source: Table 1.5.2, p36 and Table 1.5.3, p37 of Attachment 4.6 of the submission.

6.31 The proportion of patients experiencing treatment-emergent AEs across all treatment arms was higher in REGAIN ([redacted]% for galcanezumab; [redacted]% for placebo) compared to Study 295 (43.7% for 70 mg erenumab; 46.8% for 140 mg erenumab; 39.0% for placebo).

6.32 Injection site pain and nasopharyngitis were the treatment-emergent AEs, which had higher incidence in the galcanezumab-treated arms of REGAIN compared to erenumab-treated patients in Study 295.

Benefits/harms

6.33 On the basis of the direct head-to-head trial, compared with placebo galcanezumab resulted in:

- A reduction of approximately 2 migraine headache days per month (5 in the galcanezumab group and 3 in the placebo group) over a duration of exposure of 12 weeks. This reduction was observed in patients from the overall trial population, who had approximately 19 migraine headache days per month at baseline.

- For the subgroup of patients who had failed ≥3 prior medications, a reduction of approximately 5 migraine headache days per month (6 in the galcanezumab group and 1 in the placebo group) over a duration of exposure of 12 weeks. These patients had approximately 20 migraine headache days per month at baseline. The subgroup (N=104) represented 13% of the larger trial population (N=836).

6.34 On the basis of the indirect evidence presented, patients treated with Botox for 24 weeks and galcanezumab for 12 weeks would experience a similar reduction in migraine headache days per month.

Clinical claim

Galcanezumab versus Botox

6.35 The submission described galcanezumab as non-inferior in terms of comparative effectiveness, with a comparable safety profile to Botox for the treatment of patients with treatment-resistant chronic migraine.

6.36 While there were no statistically significant differences between the groups and the identified non-inferiority margin was met, there were a number of concerns with the clinical claim made by the submission:

- There were different outcome definitions and different statistical methodologies between the REGAIN and PREEMPT trials (paragraph 6.10). While the mITT analysis was intended to account for these differences, it was a post-hoc analysis.
- The differing placebo response levels between the REGAIN and PREEMPT trials suggest there were transitivity issues (paragraph 6.13).
- The treatment failure subgroup from REGAIN represented approximately 13% of the overall trial population while the subgroup from PREEMPT represented approximately 35% of that trial's overall population. The smaller proportion of the galcanezumab subgroup may impact on the transitivity of the indirect comparison (paragraph 6.6).

6.37 The ESC concluded that the magnitude of benefit observed with galcanezumab versus placebo was small and uncertain (ranging from a reduction of between 2 and 6 migraine headache days per month, from a baseline of approximately 20) and the comparative benefit versus Botox was uncertain given the transitivity issues. Comparative safety was also uncertain given the transitivity issues identified and the relative lack of data on longer-term safety for galcanezumab compared to Botox.

6.38 The PBAC noted the conclusion of non-inferiority to Botox was met across all the analyses (i.e., ITT, mITT subgroup and treatment failure subgroups) and on balance, the PBAC considered that the claim of non-inferior comparative effectiveness was reasonable. The PBAC considered the claim that galcanezumab had comparable safety to Botox was reasonably supported by the evidence presented.

Economic analysis

6.39 The submission presented a CMA over a 2-year time horizon based on the indirect comparison versus Botox. The submission indicated a 2-year time horizon was selected as this was the time horizon considered by the ESC and PBAC as the most appropriate time horizon for cost-minimisation analyses for on-going therapy (ixekizumab PSD July 2018, abatacept PSD March 2018 and cladribine November PSD 2017 PSDs). The ESC considered there are likely to be differences in the natural history of psoriatic arthritis, relapsing remitting multiple sclerosis and chronic migraine and the use of the 2 year time horizon was not well justified.

6.40 The trial-based equi-effective doses were estimated as galcanezumab 120 mg monthly and Botox 164U every 12 weeks. The results of the CMA based on the published price for Botox are provided in the table below. The ESC noted the equi-effective doses used in the CMA were galcanezumab 120 mg every 30 days = Botox 200 IU every 12 weeks.

Table 12: Results of the cost-minimisation analysis based on the published price for Botox

Component	Galcanezumab	Botox
Drug costs (AEMP)		
Per dose	$	$674.98[a]
Number of doses per 2 years	25.0	9.0
Total drug cost: 2 years	$	$6,074.82
Administration costs		
Neurologist (MBS Item 116) per visit	$	$76.65
Botox administration (MBS Item 18377) per visit	-	$124.85
Number of visits per 2 years	5.0	9.0
Total administration cost: 2 years	$	$1,813.50
Total drug and administration cost: 2 years	**$**	**$7,888.32**

[a] The cost per dose of Botox was based on the published price ($337.49 per vial) and assumed 200U (2 vials) per dose.
AEMP=approved ex-manufacturer price
Source: Table 3.4.2, p115 of the submission.

6.41 The number of administrations of galcanezumab over 2 years (25) did not correspond to the number of doses assumed when estimating the financial implications, where an average of scripts per year was assumed for new patients, including the loading dose. In addition, the analysis assumed that Botox is dosed every weeks, however the DUSC review of Botox in 2017 reported that the mean number of injection services for Botox in the first 12 months after initiation was 3.23, which on average corresponded to treatment every 16 week. The PSCR states that the number of administrations of galcanezumab used in the CMA (per year) was calculated over 2 years and in the financial estimates the number of scripts (per year) was averaged over 6 years.

6.42 The ESC noted the impact of rounding the number of Botox administrations over 2 years[2] resulted in an average of Botox administrations per year being applied in

[2] *2 x 4.33 = 8.66, rounded up to 9*

the CMA which was not consistent with the average of [redacted] applied in the financial estimates or 3.23 determined by the DUSC review. Additionally, rounding the number of administrations resulted in different durations of treatment for Botox and galcanezumab ([redacted] years vs 1.97 years, respectively).

6.43 The PBAC considered the CMA should apply the trial-based equi-effective doses i.e., galcanezumab 120 mg every 30 days = Botox 164U every 12 weeks, assume a 2 year treatment duration for galcanezumab and Botox and not round the number of doses or administrations. The revised CMA based on the published Botox price is presented below.

Table 13: Results of the cost-minimisation analysis based on the published price for Botox, revised

Component	Galcanezumab	Botox
Drug costs (AEMP)		
Per dose	$[redacted]	$553.48[a]
Number of doses per 2 years	25.35	8.70
Total drug cost: 2 years	$[redacted]	$4,813.33
Administration costs		
Neurologist (MBS Item 116) per visit	$[redacted]	$76.65
Botox administration (MBS Item 18377) per visit	-	$124.85
Number of visits per 2 years	5.0	8.70
Total administration cost: 2 years	$[redacted]	$1,752.33
Total drug and administration cost: 2 years	$[redacted]	$6,565.66

[a] The cost per dose of Botox was based on the published price ($337.49 per vial) and assumed 164IU per dose.
AEMP=approved ex-manufacturer price

Drug cost/patient/year

6.44 The table below provides a summary of the cost per dose, number of administrations per year and drug cost per patient per year based on the assumptions applied in the CMA and the financial estimates. The published price of Botox was used. The price for galcanezumab based on the CMA is higher than that for Botox as it accounts for the reduced administration costs.

Table 14: Drug cost per patient for galcanezumab and Botox (AEMP)

	Galcanezumab			Botox	
	CMA	Financial estimates: Market share patients	Financial estimates: Epi patients	CMA	Financial estimates
Cost per dose	$[redacted]			$674.98	
Total doses administered	[redacted]	[redacted]	[redacted]	4.5	4.33
Drug cost/patient/ year	$[redacted]	$[redacted]	$[redacted]	$3,037.41	$2,922.66

AEMP=approved ex-manufacturer price; CMA=cost minimisation analysis; DPMQ=dispensed price for maximum quantity
Source: Table 12 and Galcanezumab Section 4 Model.xls

Estimated PBS usage & financial implications

6.45 This submission was not considered by DUSC. A mixed model approach, with a combination of market share displacement (substitution of Botox) and an epidemiological analysis (new patients) was used to estimate the usage and financial impact of the PBS listing of galcanezumab. The market share approach contributed [redacted]% of estimated patients in Year 1 and [redacted]% over the first 6 years of listing, while the epidemiological approach contributed [redacted]% and [redacted]% of estimated patients, respectively. The PBAC noted the erenumab submission considered at the March 2019 meeting assumed only 21% of use would be from Botox patients (paragraph 7.4, erenumab PSD, March 2019).

6.46 The table below provides a summary of the estimated usage and financial implications of the listing of galcanezumab.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated						
Market share approach[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Epidemiological approach[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[c]						
Market share approach[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Epidemiological approach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of galcanezumab						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost offsets for substituted Botox	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net financial implications						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Overall net cost to Government	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]

[a] The number of patients for the market share approach is calculated by dividing the volume of Botox scripts displaced by galcanezumab by the mean services per patient per year as estimated in the 2017 DUSC report (3.23)

[b] Includes initial and continuing patients. The submission assumed [redacted]% of patients would have a response at 3 months with [redacted]% continuing for the remainder of Year 1 and 80% continuing in subsequent years.

[c] Initiating [redacted] scripts to Month 3; remainder of year [redacted] scripts; subsequent years [redacted] scripts with average of [redacted] scripts over 6 years for a responding patient.

[d] Corrected to be consistent with the financial estimates Excel workbook.

Source: Table 4.2.16, p132; Table 4.3.3, p134; Table 4.4.1, p135; Table 4.5.8, p139 of the submission and Excel workbook 'A6.1_Galcanezumab Section 4 model'.

The redacted table shows that at Year 6, the estimated number of patients was 10,000 – 50,000 and the net cost to the PBS would be $10 - $20 million per year.

6.47 The submission assumed [redacted]% of Botox scripts will be replaced by galcanezumab in Year 1, increasing to [redacted]% in Year 6. The submission calculated the number of galcanezumab scripts that will replace these Botox scripts using a script equivalence of [redacted] galcanezumab scripts for every [redacted] Botox script, assuming each patient used an average of [redacted] galcanezumab scripts per year and [redacted] Botox scripts per year. The PBAC considered the assumptions regarding script equivalence applied to the financial estimates should be consistent with the CMA (i.e., [redacted] = [redacted] instead of [redacted]).

6.48 For the epidemiological approach, the submission assumed 64% of Botox-certified neurologists in Year 1 will prescribe galcanezumab for new chronic migraine patients, 83% in Year 2 and 100% in Year 3 to Year 6. Each Botox-certified neurologist will prescribe galcanezumab for [redacted] new chronic migraine patients per year. The submission assumed there would be no prescriptions from non-Botox certified neurologists in Year 1, with the proportion prescribing galcanezumab being [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]% in years 2 to 6. Each non-Botox certified neurologist would prescribe galcanezumab for [redacted] new chronic migraine patients per year in Year 1 to 3, increasing to [redacted] in Year 4 to 6. Of the total number of new patients being treated with galcanezumab each year, a majority ([redacted]% to [redacted]%) are treated by Botox-certified neurologists.

6.49 For the epidemiological approach, the submission assumed that [redacted]% of patients would continue at the 3 month assessment. This was based on a repeated measures model estimate, sourced from the assessed ITT population of REGAIN (N=836). Continuation from Month 3 to the end of Year 1 was assumed to be [redacted]% (annual continuation rate of [redacted]% prorated to 9 months), and continuation in subsequent years was assumed to be [redacted]%. The [redacted]% was sourced from the open-label phase of REGAIN where [redacted]% of responders at month 3 had maintained ≥50% response at month 9.

6.50 The estimated net cost to Government for the first 6 years of galcanezumab listing was $30 - $60 million (based on the published Botox price). This estimate was sensitive to the proportion of patients sourced from the market share approach (replacing Botox) and new patients sourced from the epidemiological approach.

6.51 The ESC noted that a proportion of patients may use Botox and galcanezumab sequentially which has not been accounted for in the financial estimates.

6.52 Given the risk of use in a broader migraine population than requested and continued use in patients who do not meet the specified response criteria together with uncertain financial estimates, the ESC considered that a Risk Sharing Arrangement (RSA) with a [redacted]% rebate over agreed caps may be required should the PBAC recommend galcanezumab for listing on the PBS. The PBAC considered that a combined galcanezumab and Botox RSA would be appropriate in order to manage the risks identified by the ESC, and that the RSA should be based on the current Botox RSA cap only allowing for the increase of cost where this is due to switching to galcanezumab.

Quality Use of Medicines

6.53 The submission provided a summary of activities proposed to support the quality use of medicines (QUM) with galcanezumab, as well as discussion of risk management activities and pharmacovigilance activities.

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required (Streamlined) listing of galcanezumab for the treatment of chronic migraine in patients who have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications. The PBAC considered galcanezumab was an alternative treatment to Botox for patients with chronic migraine and provided a similar reduction in migraine headache days. The PBAC considered the cost minimisation analysis should be based on equi-effective doses of 120 mg galcanezumab every 30 days and 164IU of Botox every 12 weeks over 2 years of treatment. Additionally, the PBAC considered it would be appropriate for galcanezumab and Botox to be in the same risk share arrangement to ensure the galcanezumab patient population is restricted to the same high need patient population as for Botox.

7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of galcanezumab would be acceptable if it were cost-minimised against Botox.

7.3 The PBAC considered 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. The PBAC noted the larger incremental benefit of galcanezumab versus placebo when the analyses were based on the post-hoc treatment failure subgroups but considered these analyses to be less reliable than the analyses based on the ITT and mITT populations.

7.4 The PBAC considered that Botox was the appropriate main comparator. The PBAC noted the ESC considered that BSC could be an additional comparator and considered this was particularly the case for the patients identified with the epidemiological approach which comprised [redacted]% to [redacted]% of all treated patients. The PBAC further considered there was a high degree of uncertainty regarding the number of patients estimated using the epidemiological approach and the cost-effectiveness of treating these patients and that it was appropriate to restrict galcanezumab to the same high need patient population as for Botox.

7.5 The PBAC noted there were a number of transitivity and applicability issues with the indirect comparison versus Botox but that the conclusion of non-inferiority to Botox was met across all the analyses (i.e., ITT, mITT subgroup and treatment failure

subgroups), and considered that on balance, the claim of non-inferior effectiveness was supported. The PBAC noted the relative lack of data on longer-term safety for galcanezumab compared to Botox but overall, galcanezumab was well tolerated and likely to have comparable safety to Botox.

7.6 The PBAC considered the CMA should be revised to more accurately reflect the equi-effective doses proposed by the submission (i.e., 120 mg galcanezumab every 30 days and 164IU of Botox every 12 weeks) and be conducted over 2 years of treatment for both medicines.

7.7 The PBAC considered it would be appropriate for galcanezumab and Botox to be encompassed within the same Risk Sharing Arrangement for chronic migraine based on the estimated PBS utilisation across both medicines, with necessary updates to the financial estimates and application of the correct hidden effective price, with an increase in expenditure cap to reflect the higher drug cost for galcanezumab (due to reduced administration costs compared with Botox) and that the RSA should be based on the current Botox RSA cap only allowing for the increase of cost where there is a net increase in the cost estimates due to switching to galcanezumab .

7.8 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because galcanezumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over Botox, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.

7.9 The PBAC recommended that galcanezumab should not be treated as interchangeable on an individual patient basis with Botox.

7.10 The PBAC advised that galcanezumab is not suitable for prescribing by nurse practitioners.

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

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

Outcome:

Recommended.

8 Recommended listing

8.1 Add new item:

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Proprietary name and manufacturer
GALCANEZUMAB 120 mg/1 mL, pre-filled pen	2	2	0	Emgality® Eli Lilly Australia Pty Ltd

Category/Program:	General Schedule - Section 85
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Chronic migraine
Treatment phase:	Initial - loading dose
Restriction: General Schedule	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	Must be treated by a neurologist
Clinical criteria:	Patient must have experienced an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months, prior to commencement of treatment with this drug for this condition AND Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with this drug for this condition AND The treatment must not be in combination with botulinum toxin AND Patient must be appropriately managed for medication overuse headache, prior to initiation of treatment with this drug
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.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Proprietary name and manufacturer
GALCANEZUMAB 120 mg/1 mL, pre-filled pen	1	1	1	Emgality® Eli Lilly Australia Pty Ltd

Category/Program:	General Schedule - Section 85
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Chronic migraine
Treatment phase:	Initial

Restriction: General Schedule	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	Must be treated by a neurologist
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must have experienced an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months, prior to commencement of treatment with this drug for this condition AND Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with this drug for this condition AND The treatment must not be in combination with botulinum toxin AND Patient must be appropriately managed for medication overuse headache, prior to initiation of treatment with this drug
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.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Proprietary name and manufacturer
GALCANEZUMAB 120 mg/1 mL, pre-filled pen	1	1	5	Emgality® Eli Lilly Australia Pty Ltd

Treatment phase:	Continuing
Treatment criteria:	Must be treated by or in consultation with a neurologist
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine headache days per month in order to be eligible for continuing PBS-subsidised treatment AND The treatment must not be in combination with botulinum toxin AND Patient must continue to be appropriately managed for medication overuse headache

8.2 The Botox criteria should be updated to reflect the revised list of prophylactic medications.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comments

The sponsor had no comment.