7.08 GALCANEZUMAB, Injection 120 mg in 1 mL pre-filled pen, Emgality ®, Eli Lilly Australia Pty Ltd

1 Purpose of Application

1.1 The minor resubmission proposed a number of amendments to the PBAC recommendation in July 2019 to list galcanezumab for chronic migraine. The resubmission requested amendments to the cost-minimisation analysis (CMA), financial estimates and risk sharing arrangement (RSA).

2 Background

Registration status

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

Previous PBAC consideration of galcanezumab

2.2 In July 2019, 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 (defined as patients with ≥15 headache days and ≥ 8 migraine days per month) and provided a similar reduction in migraine headache days. The PBAC considered a CMA versus Botox was appropriate and should be based on equi-effective doses of 120 mg galcanezumab every 30 days and 164U 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 RSA to ensure the galcanezumab patient population is restricted to the same high need patient population as for Botox. The PBAC advised an increase in the RSA expenditure caps would be appropriate to reflect the higher drug cost for galcanezumab (due to reduced administration costs compared with Botox).

2.3 The resubmission stated that, under the conditions of the July 2019 PBAC recommendation (as outlined in paragraph 2.2), it was not commercially viable to list galcanezumab on the PBS.

Previous PBAC consideration of other CGRP inhibitors

2.4 Galcanezumab belongs to a new class of medicines called calcitonin gene-related peptide (CGRP) inhibitors. Two other CGRP inhibitors (fremanezumab and erenumab) have been previously considered by the PBAC for chronic migraine.

2.5 In March 2020, the PBAC recommended the Authority Required (Streamlined) listing of fremanezumab 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 (paragraph 6.1, fremanezumab Public Summary Document (PSD), March 2020 PBAC meeting). The PBAC recommended listing on the basis of a CMA compared to Botox with equi-effective doses of 225 mg fremanezumab every month and 164U of Botox every 12 weeks over 2 years of treatment. Additionally, the PBAC considered it would be appropriate for the use, and associated expenditure, of fremanezumab to be restricted to the same high need patient population as for Botox. Fremanezumab is not currently listed on the PBS.

2.6 In July 2018 and March 2019, the PBAC did not recommend erenumab for the treatment of chronic migraine. A resubmission for erenumab for chronic migraine was submitted for consideration at the November 2019 PBAC meeting, however was withdrawn by the sponsor prior to PBAC consideration.

Sponsor hearing

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

Consumer comments

2.8 The PBAC noted and welcomed the input from individuals (186), 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. 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.

2.9 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.

3 Requested listing

3.1 The restriction criteria recommended by the PBAC in July 2019 is provided below with additions (italics) and deletions (strikethrough) proposed by the Secretariat.

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

* Based on AEMP of $[redacted] per injection

Category/Program:	General Schedule - Section 85
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Chronic migraine
Treatment phase:	Initial ~~– loading dose –~~ *treatment covering the loading dose and doses at week 4 and week 8*
Restriction:	☒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	DPMQ	Proprietary name and manufacturer
GALCANEZUMAB 120 mg/1 mL, pre-filled pen	1	1	5	$[redacted]	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

3.2 In July 2019 the PBAC recommended two initial restriction criteria, one with a maximum quantity of 2 with 0 repeats for the induction dose and another with a maximum quantity of 1 with 1 repeat to provide a total of 12 weeks initial treatment. The Secretariat proposed a single initial restriction criteria with a maximum quantity of 2 and 1 repeat (4 injections in total) to provide 12 weeks of initial treatment. The financial estimates below are based on a maximum quantity of 1.

4 Key concerns addressed by the resubmission

4.1 The minor resubmission addressed four key concerns regarding the previous PBAC recommendation:

- Equi-effective doses and time horizon of the CMA.
- Estimated number of treated patients and financial implications of listing galcanezumab.
- Appropriateness of including galcanezumab in the Botox RSA and expenditure caps.
- Time period covered by RSA.

4.2 Each of the four key concerns are summarised in Table 1 and discussed in further detail below.

Table 1: Key concerns addressed in the minor resubmission

Key concern as identified by resubmission	PBAC recommendation (July 2019)	Sponsor's proposal to address
Equi-effective doses and cost minimisation analysis	Equi-effective doses galcanezumab 120 mg every 30 days and 164 U Botox every 12 weeks. CMA to be conducted over 2 years. Effective AEMP $[redacted] (paragraph 7.6, galcanezumab PSD, July 2019 PBAC meeting).	Equi-effective doses galcanezumab 120 mg every 30 days and 194 U Botox every 12 weeks. CMA to be conducted over 3 years Effective AEMP $[redacted] An adjustment of price at the conclusion of any RSA based clinical outcomes in the TRIUMPH study
Estimated number of treated patients and financial implications of listing galcanezumab	Galcanezumab and Botox to be in the same RSA to ensure the galcanezumab patient population is restricted to the same high need patient population as for Botox. (paragraph 7.1, galcanezumab PSD, July 2019 PBAC meeting)	Proposed a revised estimate of the number of patients expected to be treated with galcanezumab to account for significant number of eligible patients that are not currently treated with Botox.
Appropriateness of including galcanezumab in the Botox RSA and expenditure caps	Galcanezumab and Botox to be encompassed in the same risk share arrangement with an increase in expenditure caps to allow for higher drug cost for galcanezumab. (paragraph 7.7, galcanezumab PSD, July 2019 PBAC meeting).	[redacted]% of galcanezumab scripts are allocated to the Botox expenditure cap. All other scripts are allocated to separate CGRP inhibitor expenditure caps. [redacted]% increase in Botox expenditure caps to account for the higher drug cost associated with galcanezumab. Requested the PBAC consider recommending a 'maximum ceiling rebate' over the life of the Deed to ensure viability of listing.
Duration of RSA	No specific recommendation regarding duration of RSA.	Requested consideration of a 3 year duration.

AEMP approved ex-manufacturer price; CGRP calcitonin gene-related peptide; PSD public summary document; RSA risk share arrangement;

Cost-minimisation analysis

4.3 In July 2019, the PBAC considered a CMA versus Botox was appropriate and should be based on equi-effective doses of 120 mg galcanezumab every 30 days and 164U of Botox every 12 weeks over 2 years of treatment (paragraph 7.6, galcanezumab PSD, July 2019 PBAC meeting).

4.4 The resubmission proposed a revised CMA based on the following assumptions:

- Equi-effective doses galcanezumab 240 mg loading dose followed by 120 mg every 30 days and Botox 194U every 12 weeks
- Over a 2 year period, patients treated with galcanezumab visit a neurologist once and a general practitioner 3.5 times. Patients treated with Botox visit a neurologist 8.7 times and incur administration costs at each visit. This is consistent with the fremanezumab recommendation (paragraph 6.8, fremanezumab PSD, March 2020 PBAC meeting).

- Three year time horizon (with neurologist and general practitioner costs for the 2 year period based on the costs above divided by 2 and multiplied by 3).

4.5 The CMA based on the effective price of Botox (which was provided to the sponsor following the July 2019 recommendation) is summarised in Table 2.

Table 2: CMA proposed in the resubmission

Component	Galcanezumab	Botox
Drug costs (AEMP)		
Pack	1 x 140 mg injection	1 x 100U vial
Cost per pack	$ [redacted]	$ [redacted]
Number of packs per dose	1.0	1.94
Cost per dose	$ [redacted]	$ [redacted]
Number of doses per 3 years	37.53[1]	13.04[2]
Total drug cost: 3 years	$ [redacted]	$ [redacted]
Administration costs		
Neurologist (MBS Item 116) per visit	$79.05	$79.05
Botox administration (MBS Item 18377) per visit	-	$128.75
Number of visits per 3 years	1.5[3]	13.04[5]
General practitioner MBS (Item 23)	$38.75	$38.75
Number of visits per 3 years	5.25[4]	-
Total administration cost: 3 years	$322.01	$2,771.79
Total drug and administration cost: 3 years	$ [redacted]	$ [redacted]

AEMP approved ex-manufacturer price; MBS Medicare Benefits Schedule

1. Calculated as (365.25x3)/30+1
2. Calculated as (8.7/2)*3
3. Calculated as (1/2)*3
4. Calculated as (3.5/2)*3

4.6 The resubmission stated the previous submission for galcanezumab was based on a Botox equi-effective dose of 194U; however, the submission considered by PBAC in July 2019 proposed equi-effective doses of galcanezumab 120 mg monthly and Botox 164U every 12 weeks (paragraph 6.40, galcanezumab PSD, July 2019 PBAC meeting). The CMA presented in the July 2019 submission assumed 2 vials of Botox (i.e. 200U) were administered for each dose.

4.7 The resubmission stated the equi-effective dose of Botox (194U) was based on a previous DUSC review (Botox PSDs, July 2013 and March 2018 PBAC meetings; Botox DUSC Public Release Document, June 2017*)*; however, this value could not be verified in the stated references*. The pre-PBAC response acknowledged the equi-effective dose of Botox should be 193U.* The fremanezumab submission considered in November 2019 proposed an equi-effective dose for Botox based on the average number of Botox vials dispensed per service (paragraph 6.64, fremanezumab PSD, November 2019 PBAC meeting); however, the ESC considered equi-effective doses should be based on the clinical trial evidence used to determine non-inferiority and recommended an equi-effective dose for Botox of 164U.

4.8 A number of sensitivity analyses were conducted by the Secretariat, varying the CMA inputs as summarised in Table 3.

Table 3: Sensitivity analyses conducted by Secretariat (changes to base case in underlined)

Scenario	Equi-effective dose	Time horizon of CMA	AEMP
Base case	GAL 240 mg loading dose followed by 120 mg every 30 days and Botox 194U every 3 months	3 years	$[redacted]
SA 1: as recommended by PBAC	GAL 240 mg loading dose followed by 120 mg every 30 days and Botox 164U every 3 months	2 years	$[redacted]*
SA 2: equi-effective dose as recommended by PBAC and 3 year time horizon	GAL 240 mg loading dose followed by 120 mg every 30 days and Botox 164U every 3 months	3 years	$[redacted]
SA 3: Assuming 2 vials of Botox per dose (as included in CMA in July 2019 submission)	GAL 240 mg loading dose followed by 120 mg every 30 days and Botox 200U every 3 months	3 years	$[redacted]

AEMP approved ex-manufacturer price; CMA cost-minimisation analysis; GAL galcanezumab; SA sensitivity analysis

* The resubmission stated the AEMP recommended by the PBAC was $[redacted]; however this calculation was conducted over 3 years and did not incorporate a number of changes recommended by the PBAC (for example, GP visits).

4.9 The resubmission proposed the equi-effective dose of Botox would be revised based on the outcomes for galcanezumab from an observational study (TRIUMPH). The outcomes from TRIUMPH would be compared to the outcomes in the pivotal study (REGAIN) considered by the PBAC in July 2019 and the price of galcanezumab would be recalculated at the end of the Deed using revised equi-effective doses of Botox, which would vary depending on the clinical outcomes for TRIUMPH.

Estimated number of treated patients and financial estimates

4.10 The resubmission provided a Section 4 'Utilisation and cost model workbook' consistent with a previous version of the template but modified to add risk-sharing elements including a two-cap system described below. The resubmission stated that due to the complexity of the proposed RSA and the modelling required, the model is macro-enabled. The Secretariat noted the spreadsheet was complex, not in the format required for consideration by other relevant agencies) and, as a minor submission, the estimates were not evaluated.

4.11 The resubmission stated the appropriate approach to developing expenditure caps and an RSA for the CGRP inhibitors is to "attempt to set *high* discount levels at a *reasonable* estimate of the maximum eligible population". The resubmission stated that the estimated number of patients with treatment-resistant chronic migraine presented in the resubmission (330, 643 in Year 6) is more conservative than previous DUSC estimates of patient numbers. The resubmission noted that the DUSC, during its previous evaluation of the erenumab submission, considered "while the total number of patients which chronic migraine is difficult to estimate, the prevalence….is likely to be approximately 400,000 patients" (paragraph 4.3, erenumab PSD, March 2019 PBAC meeting).

4.12 The resubmission applied assumptions for the prevalence of migraine (14.64% of people over 18 years of age), the proportion of patients with chronic migraine (10%) and the proportion of patients who have failed 3 or more prior treatments (12%) that were consistent with the July 2019 submission.

4.13 The resubmission presented modelling to determine the number of treated patients incorporating a number of assumptions:

- The prevalent Botox population at the time of galcanezumab PBS listing is assumed to be 10,000 to < 20,000 based on PBS data and modelled initiations and drop-offs. The model then assumed (MS market share approach):
  - 35% of the prevalent Botox population are 'captured' by galcanezumab over 36 months.
  - 30% (Year 1) to 50% (Year 6) of the net increase in Botox initiations are 'captured' by galcanezumab each year.
- Of the remaining prevalent treatment-resistant chronic migraine patients (i.e., those not treated with Botox), between 21% (Year 1) and 6% (Year 6) elect treatment with galcanezumab (epidemiology approach).
- The model applied post-failure switch assumptions with patients switching between CGRP inhibitors, between CGRP inhibitors and Botox and some discontinuing from both treatments. The resubmission acknowledged it was likely other CGRP inhibitors would be listed on the PBS and stated that a "single CGRP persistence" was applied to galcanezumab to account for patients switching between CGRP inhibitors.
- Persistence for Botox was estimated using PBS data. For galcanezumab persistence it was assumed that, on a monthly basis, the incremental loss of patients versus the previous month is only 80% of the incremental loss of Botox for that month. The resubmission stated the galcanezumab persistence was estimated to be approximately 6% to 12% higher relative to Botox; however, no clinical evidence or expert opinion was provided to support this assumption.

4.14 The PBAC recalled the July 2019 submission assumed 27.6% patients responded to galcanezumab at 3 months and continued treatment, consistent with the clinical trial data presented (paragraph 6.49, galcanezumab PSD, July 2019 PBAC meeting). The PBAC noted a continuation rate had not been included in the financial modelling provided with the resubmission but rather the model applied monthly persistence rates. The PBAC noted the persistence rates applied to the financial estimates for galcanezumab were high (Table 4).

Table 4: Persistence rates applied to the financial estimates

	End of Year 1	End of Year 2	End of Year 3	End of Year 4	End of Year 5	End of Year 6
Botox rate in resubmission	58%	42%	36%	30%	25%	25%
GAL rate in resubmission	86%	77%	71%	67%	63%	61%

GAL galcanezumab; CGRPi calcitonin gene-related peptide inhibitor
Source: Row 40 and 41, 9. Persistency & Uptake worksheet.

4.15 The estimated number of patients initiating on galcanezumab in the first year of listing on the PBS is summarised in Table 5.

Table 5: Estimation of number of patients initiating treatment with galcanezumab in Year 1

	Value	Year 1[a]	Source and comment
Patients estimated using epidemiology approach			
Australian population ≥ 18 years of age		[redacted][1]	ABS population projection, 2012 to 2021. Consistent with July 2019 submission
Prevalence of migraine	14.64%	[redacted][2]	Weighted average of ages >=15 to 65+ (Stark 2007). Consistent with July 2019 submission
Proportion with chronic migraine	10%	[redacted][3]	Erenumab PSD, July 2018 PBAC meeting. Consistent with July 2019 submission
Proportion failed 3 or more prior treatments	12%	[redacted][4]	Total of patients who had been prescribed >=3 (12%) lines of preventative treatment (Ford 2017) .Consistent with July 2019 submission
Patients initiating GAL: epidemiology		[redacted][5]	Total number of loading doses [Cell T11, 3a.Volumes CGRP EPI worksheet]
Patients initiating GAL: MS approach		[redacted][6]	Total number of loading doses [Cell T11, 3a.Volumes CGRP MS worksheet]
TOTAL number of patients initiating treatment with GAL		[redacted][5]	[redacted][5]+ [redacted][6]

GAL galcanezumab; MS market share; PSD public summary document

[a] Number of treated patients estimated at each step in Year 1 of the financial estimates.

The redacted values correspond to the following ranges:

[1]>10,000,000

[2]3,000,000 to <4,000,000

[3]300,000 to <400,000

[4]30,000 to <40,000

[5]5,000 to <10,000

[6]500 to <5,000

4.16 The estimated total number of prevalent patients with treatment-resistant chronic migraine and the number treated with galcanezumab and Botox is summarised in Table 6.

Table 6: Estimation of number of prevalent treatment-resistant chronic migraine patients and number treated with Botox and galcanezumab

	2021	2022	2023	2024	2025	2026
Number of patients number of chronic migraine patients who have failed ≥ 3 treatments	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Without galcanezumab listing						
Number of patients treated with Botox	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]
% Eligible Population Treated	31%	36%	39%	43%	47%	50%
With galcanezumab listing						
Number of patients treated with Botox	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Number of patients initiating treatment with galcanezumab	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]
Number of patients treated with galcanezumab	[redacted][5]	[redacted][4]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]
Total Patients Treated	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][6]	[redacted][6]
% Eligible Population Treated	36%	54%	66%	73%	78%	82%

Source: Tables 4.2, 4.7 of resubmission; Cells C27 to H27, 2a.Patients CGRP EPI worksheet
The redacted values correspond to the following ranges:
[1]*30,000 to <40,000*
[2]*10,000 to <20,000*
[3]*20,000 to <30,000*
[4]*5,000 to <10,000*
[5]*500 to <5,000*
[6]*30,000 to <40,000*

4.17 The resubmission stated that, without the availability of galcanezumab (or an alternative CGRP inhibitor), 50% of patients with treatment-resistant chronic migraine would remain untreated in 2026. The resubmission indicated the reasons for under-treatment included difficulty accessing neurologists for Botox, the need to travel long distances to access treatment and financial factors including limited access to public or bulk billing facilities. The resubmission quoted the Australian and New Zealand Headache Society that "overall, the CGRP antibodies have the potential to allow more equitable access to effective treatment for chronic migraine".

4.18 The estimated number of scripts and net cost of listing galcanezumab on the PBS/ RPBS for chronic migraine is provided in Table 7. A summary of the net cost for the high case and the submission considered in July 2019 is also provided.

Table 7: Estimated use and financial implications: base case, high case and submission considered July 2019 for chronic migraine

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base case						
Number of scripts dispensed	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]
Cost of galcanezumab	$[redacted][4]	$[redacted][5]	$[redacted][6]	$[redacted][7]	$[redacted][7]	$[redacted][8]
Cost of Botox	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Net cost to the PBS/RPBS[1]	$[redacted][4]	$[redacted][5]	$[redacted][6]	$[redacted][7]	$[redacted][7]	$[redacted][7]
High case						
Net cost to the PBS/RPBS[1]	$[redacted][9]	$[redacted][7]	$[redacted][8]	$[redacted][10]	$[redacted][11]	$[redacted][11]
Submission considered July 2019						
Net cost to the PBS/RPBS[2]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][9]

1. November 2020 chronic migraine: calculated using galcanezumab AEMP $[redacted] and Botox AEMP $[redacted]
2. July 2019 chronic migraine: calculated using galcanezumab AEMP $[redacted] and Botox AEMP $[redacted]

Source: Scripts – Row 40, 3d.Impact CGRP EFF; Cost of galcanezumab: Row 25, 3d. Impact CGRP EFF; Row 26, Cost Botox: 4b. Displaced EFF; Net cost: Row, 18, 7. Net changes Health.

The redacted values correspond to the following ranges:
[1] 40,000 to < 50,000
[2] 100,000 to < 200,000
[3] 200,000 to < 300,000
[4] $0 to < $10 million
[5] $20 million to < $30 million
[6] $30 million to < $40 million
[7] $40 million to < $50 million
[8] $50 million to < $60 million
[9] $10 million to < $20 million
[10] $60 million to < $70 million
[11] $70 million to < $80 million

4.19 The net cost to the PBS/RPBS of listing galcanezumab (including offsets due to a reduction in the use of Botox) was estimated to be $40 million to < $50 million in Year 6, and a total of $100 million to < $200 million in the first 6 years of listing. The PBAC noted the net cost to the PBS/ RPBS excluding offsets was $200 million to < $300 million in the first 6 years of listing.

4.20 The resubmission presented a 'high case scenario' that assumed a higher proportion of patients would be treated. This scenario assumed (i) the proportion of prevalent patients captured by galcanezumab increased from 35% over 36 months to 80% over 24 months (ii) the proportion of the net increase in Botox initiations captured increased from 30% in Year 1 (and 50% in Year 6) to 60% in Year 1 (and 90% in Year 6) and (iii) the proportion of patients not treated with Botox treated with galcanezumab increased from 21% in Year 1 (and 6% in Year 6) to 35.3% in Year 1 (and 8.5% in Year 6).

4.21 The high case scenario estimated 10,000 to < 20,000 patients would initiate treatment with galcanezumab in Year 1 (compared to 7,480 in the base case scenario) and a total of 30,000 to < 40,000 patients would be treated with galcanezumab in Year 6 (compared to 20,000 to < 30,000 in the base case scenario). The net cost of listing galcanezumab on the PBS over the first six years for the high case scenario was estimated to be $300 million to < $400 million including Botox offsets and $300 million to < $400 million excluding Botox offsets.

4.22 The resubmission acknowledged the challenges associated with estimating the number of patients that may be treated with this new class of medicine and considered any RSA "needs to be both affordable to the Commonwealth and commercially viable for the sponsor".

Risk sharing arrangement

4.23 In July 2019, the PBAC considered it would be appropriate for galcanezumab and Botox to be in the same RSA to ensure the galcanezumab patient population is restricted to the same high need patient population as for Botox. Correspondence from the Australian and New Zealand Headache Society (ANZHS) provided with the resubmission stated "constraining availability of Botox and CGRP inhibitors to the level of the current Botox cap, while no doubt economically attractive, is not rational when assessed on purely clinical grounds".

4.24 The resubmission proposed a 'two cap' system for galcanezumab with some expenditure included in the current Botox cap and some included in a new CGRP inhibitor cap. To inform the 'two cap' approach, the resubmission sought advice from the ANZHS on whether there were potential differences in patient characteristics between a Botox patient and a CGRP inhibitor patient that may direct a choice between the two treatments. The ANZHS advice provided included the following statements:

- "We do not believe that there are any reliable clinical predictors that one or other strategy will produce a better response";
- "In practice, one or other option will be chosen and the response monitored. An inadequate response would suggest that the patient be switched to the other option".

4.25 The resubmission proposed that [redacted]% of the galcanezumab script volume would be included in the Botox expenditure caps (rather than the galcanezumab expenditure caps). The sponsor proposed allocating galcanezumab prescriptions to either the galcanezumab expenditure cap or the Botox expenditure cap based on what treatment a patient was receiving 6 months after initiation of galcanezumab (i.e., in month 7). The resubmission stated that while this could be determined with prescription data, a nominal [redacted]% allocation of galcanezumab script volume was considered reasonable based on the modelling provided.

4.26 The resubmission proposed the Botox expenditure caps be increased by [redacted]%[1] consistent with the PBAC recommendation that allowed for an increase in the Botox cap to reflect the higher drug cost for galcanezumab. The Botox Tier 1 expenditure cap would increase from $[redacted] to $[redacted] and the Tier 2 expenditure cap would increase

[1] Based on the difference in drug cost in Table 2, calculated as $[redacted] / $[redacted]

from $[redacted] to $[redacted]. The rebate between Tier 1 and Tier 2 would remain as [redacted]% with [redacted]% rebate for expenditure over Tier 2. The resubmission acknowledged that increasing the entire expenditure cap by [redacted]% is higher than the increase in costs due to [redacted]% of galcanezumab scripts being allocated to the caps (paragraph 4.25). However, the resubmission considered this was justified based on the significant concern that the current Botox cap is potentially one reason that there are currently no CGRP inhibitors listed on the PBS.

4.27 The resubmission proposed a RSA with expenditure caps for galcanezumab as summarised in Table 8. The resubmission stated the expenditure caps were selected to span the base case and high case volume estimates and significantly reduce the risk of withdrawal from the market for commercial reasons.

Table 8: Proposed galcanezumab expenditure caps

	Tier Min	Tier Max	% rebate for this tier
		$[redacted]	[redacted]%
Financial Cap Tier 1	$[redacted]	$[redacted]	[redacted]%
Financial Cap Tier 2	$[redacted]		[redacted]%

Source: Table 4.1, page 21 of resubmission

4.28 The resubmission considered there was a significant risk of the sponsor not being able to continue to supply galcanezumab for commercial reasons (referred to in the resubmission as an "access failure") with a 6 year RSA and requested the PBAC consider recommending a 3 year RSA could be negotiated.

4.29 The resubmission requested the PBAC consider recommending a "Maximum Ceiling Rebate" to mitigate the risk associated with the low patient number cap, high discount level and strong likelihood of initiating a large untreated population. The maximum ceiling rebate is proposed as the cumulative maximum dollar amount payable as a rebate over the life of the deed period. It was proposed the PBAC would recommend this mechanism but the details would be negotiated with the Commonwealth during post-PBAC pricing processes.

5 PBAC Outcome

5.1 The PBAC provided further advice in regard to its July 2019 recommendation for the listing of galcanezumab for the treatment of chronic migraine. The PBAC considered galcanezumab was cost effective if cost-minimised to Botox. The PBAC considered a separate risk sharing arrangement for galcanezumab was reasonable, however advised revisions to the financial estimates, expenditure caps and rebate levels would be required to ensure cost-effective use.

5.2 The PBAC considered the equi-effective doses were galcanezumab 240 mg as a loading dose followed by 120 mg every 30 days and Botox 164U every 3 months. The PBAC considered that, consistent with the galcanezumab recommendation in July 2019 and the fremanezumab recommendation in March 2020, it remained appropriate to base the equi-effective doses on the clinical trial evidence that was used to support non-inferiority. The PBAC noted that an average dose of Botox of 164U would require an

average of two vials and considered it reasonable for the cost-minimisation analysis to include the cost of two vials. The PBAC noted this was consistent with July 2013 consideration for Botox in which the economic analysis assumed 2 vials per administration (paragraph 6.39, Botox PSD, March 2018). The PBAC noted that a comparison of the outcomes from REGAIN and TRIUMPH (paragraph 4.9) would not inform the equi-effective doses of galcanezumab or Botox and was unlikely to be informative. The PBAC noted that conducting the cost-minimisation analysis over a 2 or 3 year time period had minimal impact on the result and considered a 3 year time horizon to be reasonable.

5.3 The PBAC considered the estimated number of patients likely to initiate treatment with galcanezumab, as outlined in Table 6, was reasonable. The PBAC noted that over the first three years of listing, approximately half of the eligible prevalent patient pool would initiate treatment with galcanezumab.

5.4 The PBAC noted the persistence rates applied to the financial estimates for galcanezumab were based on the persistence observed for Botox (using utilisation data) with a higher rate assumed due to better persistence relative to Botox and to account for use of a second CGRP inhibitor (paragraph 4.13). The PBAC considered the rates were overestimated and not consistent with the proposed restriction criteria which only allows for people with a 50% reduction in MHD to continue treatment with galcanezumab. The PBAC noted there are currently no CGRP inhibitors listed on the PBS and it was not reasonable to include higher persistence due to sequential treatment with a second CGRP inhibitor in the financial estimates. The PBAC considered the magnitude of the galcanezumab persistence benefit compared with that for Botox was not well supported.

5.5 The PBAC considered it would be reasonable for any assumptions regarding continuation and persistence to be consistent with those applied to Botox during its consideration in July 2013. The PBAC recalled that its consideration for Botox was based on the assumption that 37% to 42% of patients would achieve a 50% reduction in headache days at 24 weeks (paragraph 6.20, Botox PSD, March 2018 PBAC meeting) and the proportion of patients persisting with therapy at other assessment time points was also based on the Botox clinical trial data.

5.6 The PBAC considered the assumptions used to model Botox usage (with and without galcanezumab being PBS listed) and the proportion of Botox patients that would be treated with galcanezumab were not adequately supported and therefore the estimated Botox offsets were highly uncertain. The PBAC considered that, in view of the advice from the ANZHS that patients may switch between Botox and CGRP inhibitors (paragraph 4.24), it may be reasonable to assume no offsets for reduced Botox use would be realised once galcanezumab is listed on the PBS.

5.7 The PBAC considered the request for an RSA with expenditure caps separate to Botox was reasonable as there was likely to be a significant pool of prevalent patients with chronic migraine that would qualify for treatment with galcanezumab but were not

currently being treated with Botox. The PBAC noted the financial model provided with the resubmission was overly complicated in part due to the proposal to include a proportion of the galcanezumab volume in the Botox expenditure cap. The PBAC considered that, in light of a separate RSA, a complicated model was no longer necessary and revised financial estimates using the current Section 4 'Utilisation and cost model workbook' template will be required to progress PBS listing.

5.8 The PBAC considered that the revised financial estimates should be based on:

- Number of initiating patients as per the base case with 5,000 to < 10,000 patient initiating in Year 1 and 500 to < 5,000 in Year 6.
- Initiation criteria allowing for 2 injections with 1 repeat (12 weeks treatment), and continuing criteria 1 injection with 5 repeats; and
- 40% of patients achieving a 50% reduction in migraine headache days at Week 12, 95% of responding patients continuing treatment each subsequent year.

5.9 The PBAC considered it would be appropriate for the galcanezumab RSA, including expenditure caps and rebates, to be structured in a similar way to the Botox RSA. The PBAC considered it would be appropriate for the Tier 1 Cap for galcanezumab to be set at the level for the updated financial estimates as per paragraph 5.8. The PBAC recalled the experience with the utilisation of Botox in this indication and considered that it would be appropriate for the Tier 2 expenditure caps to be based on the assumption that 60% of patients achieve a 30% reduction in migraine headache days at the response assessment time point. The PBAC considered that the rebate between Tier 1 and Tier 2 should be [redacted]% with a [redacted]% rebate for expenditure over Tier 2.

5.10 The PBAC considered an RSA of 3 years duration would not adequately manage the risks to the Commonwealth associated with the proposed listing of galcanezumab, and that a standard 5 year RSA would be required to manage the risk of use that is not cost effective use of galcanezumab over the forward years. The PBAC noted the request to recommend a 'maximum ceiling rebate' but considered this was not consistent with the intent of expenditure caps and RSAs.

5.11 The PBAC recalled it had previously considered fremanezumab non-inferior to galcanezumab in terms of effectiveness and safety and that the equi-effective doses were fremanezumab 225 mg every month and galcanezumab 240 mg initially followed by 120 mg every month (paragraph 6.9, fremanezumab PSD, March 2020 PBAC meeting.

5.12 The PBAC recommended that galcanezumab should not be treated as interchangeable on an individual patient basis with Botox but could be treated as interchangeable on an individual patient basis with fremanezumab should both be listed on the PBS.

5.13 The PBAC considered that should another CGRP inhibitor be listed on the PBS the restriction for all CGRP inhibitors should be amended to exclude sequential use

(except in the circumstance of intolerance) until such time evidence is provided to the PBAC to demonstrate the clinical benefit and cost-effectiveness of sequential use.

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

Outcome:
Advised

6 Recommended listing

6.1 Add new medicinal product as per the July 2019 PBAC meeting recommendation, but with the following updated PBS-listing:

MEDICINAL PRODUCT medicinal product pack		**PBS item code**	**Max. Qty (packs)**	**Max. Qty (units)**	**No. of repeats**	**Available brands**
GALCANEZUMAB galcanezumab 120 mg/1 mL injection, 1 mL pen device		NEW	2	2	1	Emgality
Restriction summary [new]:						
Concept Id: (for internal Dept. use)	**Category/Program:** Section 85 - General Schedule – Code (GE)					
	Prescriber type: ☒ Medical Practitioners					
	Restriction type/ method: ☒Authority Required – immediate/real time assessment by Services Australia (telephone/online)					
	PBS indication: Chronic migraine					
	Treatment phase: Initial treatment covering the loading dose and doses at week 4 and week 8					
	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 by his or her practitioner 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					
	Prescriber instructions: Patient must have the number of migraine days per month documented in their medical records.					
	Administrative advice:					
	No increase in the maximum quantity or number of units may be authorised.					
	No increase in the maximum number of repeats may be authorised.					

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Qty (packs)	Max. Qty (units)	No. of repeats	Available brands
GALCANEZUMAB galcanezumab 120 mg/1 mL injection, 1 mL pen device	NEW	1	1	5	Emgality

Restriction summary [new]	
Concept Id: (for internal Dept. use)	**Category/Program:** Section 85 - General Schedule – Code (GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type/ method: ☒ Authority Required – immediate/real time assessment by Services Australia (telephone/online)
	PBS indication: Chronic migraine
	Treatment phase: Continuing treatment from week 12 onwards
	Treatment criteria:
	Must be treated by a specialist neurologist or in consultation with a specialist 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 days per month
	AND
	The treatment must not be in combination with botulinum toxin
	AND
	Patient must continue to be appropriately managed for medication overuse headache
	Prescriber instructions: Patient must have the number of migraine days per month documented in their medical records.
	Administrative advice:
	No increase in the maximum quantity or number of units may be authorised.
	No increase in the maximum number of repeats may be authorised.

6.2 As a flow-on change, update the list of prophylactic migraine medications in the botulinum toxin type A chronic migraine listing (PBS item code 11000Y, Treatment of Concept: 5262) to match that above (concept Id 24842).

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

7 Context for Decision

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

8 Sponsor's Comment

Lilly thanks the Committee for its deep consideration and updated recommendation and all stakeholders for their feedback and input relating to this minor submission.