

7.01 ERENUMAB,

**Solution for subcutaneous injection 70 mg in 1 mL
single dose pre-filled pen**

**Solution for subcutaneous injection 140 mg in 1 mL
single dose pre-filled pen,**

Aimovig[®],

Novartis Pharmaceuticals Australia Pty. Limited

1 Purpose of submission

- 1.1 The Standard Re-entry submission requested General Schedule Authority Required (STREAMLINED) listing for erenumab for the prophylaxis of adults with chronic migraine who have experienced an inadequate response, intolerance or a contraindication to at least 3 prophylactic migraine medications.
- 1.2 The basis for the resubmission was a claim of non-inferiority against galcanezumab, fremanezumab and eptinezumab, supported by an indirect treatment comparison using placebo as the common comparator. The resubmission presented a cost-minimisation approach versus galcanezumab and fremanezumab.
- 1.3 Table 1 presents the key components of the clinical issue addressed by the resubmission.

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

Component	Description
Population	Patients with chronic migraine who have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications.
Intervention	Erenumab 140 mg SC or 70 mg SC every 4 weeks.
Comparator	Galcanezumab 120 mg SC once monthly, with a 240 mg loading dose. Fremanezumab 225 mg SC once monthly. Eptinezumab 100 mg IV every 12 weeks.
Outcomes	Change from baseline in the number of monthly migraine days, proportion of responders ($\geq 50\%$ reduction in monthly migraine days), and overall safety outcomes.
Clinical claim	Erenumab is non-inferior in terms of comparative efficacy and non-inferior in terms of comparative safety when compared to galcanezumab, fremanezumab and eptinezumab.

Source: Table 1.1, p2 of the resubmission; Para. 1.2, Erenumab, PSD, July 2018 PBAC meeting; Para. 1.2, Erenumab, PSD, March 2019 PBAC meeting.

SC = subcutaneous; IV = intravenous.

2 Background

Registration status

- 2.1 Erenumab was listed on the Australian Register of Therapeutic Goods on 2 July 2018 for 'prophylaxis of migraine in adults'.

Previous PBAC consideration

- 2.2 Erenumab was previously considered by the Pharmaceutical Benefits Advisory Committee (PBAC) for chronic migraine in July 2018 and March 2019. The comparator was botulinum toxin type A in July 2018 and botulinum toxin type A and best supportive care (BSC) in the March 2019 submission.
- 2.3 Since 2019, 3 calcitonin gene-related peptide (CGRP) medications, galcanezumab, fremanezumab and eptinezumab have been listed on the PBS for the treatment of chronic migraine:
- In July 2019, the PBAC recommended the Authority Required listing of galcanezumab for the treatment of chronic migraine in patients who have experienced an inadequate response, intolerance or a contraindication to at least 3 prophylactic migraine medications. In November 2020, the PBAC provided further advice regarding the economic approach, financial estimates and risk-sharing arrangement. Galcanezumab was listed on the PBS for chronic migraine on 1 June 2021.
 - In March 2020, the PBAC recommended the Authority Required listing of fremanezumab for the treatment of chronic migraine in patients who have experienced an inadequate response, intolerance or a contraindication to at least 3 prophylactic migraine medications. Fremanezumab was listed on the PBS for chronic migraine on 1 August 2021. The PBAC previously considered that fremanezumab was non-inferior to galcanezumab in terms of effectiveness and safety and that the equi-effective doses were fremanezumab 225 mg every month and galcanezumab 240 mg initially followed by 120 mg every month (paragraph 5.11, Galcanezumab Public Summary Document [PSD], November 2020 PBAC meeting).
 - In March 2022, the PBAC recommended amending the current PBS listing of galcanezumab for chronic migraine to include the treatment of patients with high-frequency episodic migraine (HFEM) by removing the criteria for patients to have an average of 15 or more headache days per month. Galcanezumab is not currently listed on the PBS for HFEM.
 - In July 2022, the PBAC recommended the Authority Required listing of eptinezumab for the treatment of chronic migraine in patients who have had an inadequate response, intolerance or contraindication to 3 or more prior prophylactic therapies for chronic migraine. The PBAC considered eptinezumab to be non-inferior to galcanezumab and fremanezumab in terms of effectiveness and safety. The equi-effective doses were eptinezumab 100 mg every 12 weeks, galcanezumab 240 mg initially then 120 mg every month, fremanezumab 225 mg every month (paragraphs 7.1, 7.2, and 7.5, Eptinezumab PSD, July 2022 PBAC meeting). Eptinezumab was listed on the PBS for chronic migraine on 1 June 2021.

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- In November 2022, the PBAC recommended amending the PBS listing of fremanezumab 675 mg quarterly to treatment-resistant migraine, defined as at least 8 migraine headache days per month (includes chronic migraine and HFEM). In August 2023, the PBAC extended this recommendation to the PBS listing of fremanezumab 225 mg monthly. The PBS listing was changed on 1 November 2023.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ERENUMAB					
Initial treatment					
Erenumab 70 mg in 1.0mL solution for injection, pre-filled pen	\$ █████ published price \$ ^a effective price	1	1	2	Aimovig
Erenumab 140 mg in 1.0mL solution for injection, pre-filled pen	\$ █████ published price \$ ^a effective price	1	1	2	Aimovig
Continuing treatment					
Erenumab 70 mg in 1.0mL solution for injection, pre-filled pen	\$ █████ published price \$ ^a effective price	1	1	5	Aimovig
Erenumab 140 mg in 1.0mL solution for injection, pre-filled pen	\$ █████ published price \$ ^a effective price	1	1	5	Aimovig

^a To be determined based on the results of the cost minimisation approach.

Category / Program: General Schedule
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Episodicity: Chronic
Condition: Chronic migraine
Indication: Chronic migraine
Treatment Phase: Initial Treatment Phase
Clinical criteria:
Patient must have experienced an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months, prior to commencement of treatment with this medicine for this condition,
AND
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
Patient must be appropriately managed by his or her practitioner for medication overuse headache, prior to initiation of treatment with this drug
Treatment criteria:
Patient must be treated by a neurologist
AND
Patient must not be undergoing concurrent treatment with the following PBS benefits: (i) botulinum toxin type A listed for this PBS indication, (ii) another drug in the same pharmacological class as this drug listed for this PBS indication.
Population criteria:
Patient must be aged 18 years or older
Prescribing Instructions:

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Prophylactic migraine medications are propranolol, amitriptyline, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate or topiramate
AND
Patient must have the number of migraine days per month documented in their medical records

Category / Program: General Schedule
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
Administrative Advice: {Insert any Administrative Advice proposed by the submission}
Episodicity: Chronic
Condition: Chronic migraine
Indication: Chronic migraine
Treatment Phase: Continuing Treatment Phase
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
Patient must continue to be appropriately managed for medication overuse headache.
Grandfathering
Patient has received erenumab treatment prior to PBS listing date, and must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine days per month after three treatment cycles (12 weeks duration) in order to be eligible for subsequent continuing PBS-subsidised treatment;
Treatment criteria:
Patient must be treated by a neurologist
AND
Patient must not be undergoing concurrent treatment with the following PBS benefits: (i) botulinum toxin type A listed for this PBS indication, (ii) another drug in the same pharmacological class as this drug listed for this PBS indication.
Prescribing Instructions:
Patient must have the number of migraine days per month documented in their medical records

- 3.1 The submission requested the listing of both the 70 mg and 140 mg strengths of erenumab. The TGA Product Information stated that the recommended dose of erenumab is 70 mg every 4 weeks but that some patients may benefit from a dosage of 140 mg every 4 weeks. The resubmission claimed that the availability of both doses on the PBS will allow for physician discretion and patient choice when selecting a preferred strength.
- 3.2 The proposed published dispensed price for maximum quantity (DPMQ) for both strengths of erenumab (\$| for one injection) was significantly higher than fremanezumab (\$560.39 for one injection) and galcanezumab (initial: \$1037.61 for two injections; continuing: \$523.03 for one injection).
- 3.3 The proposed PBS restrictions were consistent with the PBS listings for galcanezumab for chronic migraine. The PBS indication for fremanezumab was amended in August 2023 to treatment-resistant migraine, defined as at least 8 migraine headache days per month.

- 3.4 The proposed PBS restriction was narrower than the TGA indication, which only required patients to have at least 4 migraine days per month, did not require patients to have failed or be contraindicated to any prophylactic/preventive medications and included patients with episodic migraine.
- 3.5 The proposed PBS restrictions were consistent with clinical evidence provided (pre-specified and *post-hoc* subgroup analyses), and the financial estimates, which used a mixed epidemiology and market share approach to account for the expansion of the fremanezumab PBS listings to include HFEM.
- 3.6 The resubmission proposed a grandfather clause. The resubmission claimed there were around < 500 patients currently receiving erenumab as a part of the access program in Australia. The grandfather clause would also allow patients who were obtaining erenumab privately to transition to PBS-subsidised treatment.

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

4 Population and disease

- 4.1 Migraine is a primary headache disorder, characterised by recurrent headaches lasting 4-72 hours and often accompanied by symptoms such as nausea, vomiting and hypersensitivity to light (photophobia) and sound (phonophobia). The headache attack itself is often preceded by non-specific prodromes, sensory warning symptoms immediately prior to the headache attack (aura) and a non-specific postdrome phase that can last various days. Due to these symptoms, patients report substantial impairment in their ability to perform daily or physical activities, attend school/work and function socially.
- 4.2 Approximately 10% of the adult population is affected by migraine worldwide (Lipton et al, 2007;¹ Stovner & Andree, 2010²). The PBAC previously considered a migraine prevalence of 14.64% based on Stark et al. (2007)³ was reasonable (paragraph 7.6, Galcanezumab PSD, March 2022 PBAC meeting).
- 4.3 The resubmission identified the target population as patients with chronic migraine, defined as patients experiencing an average of 15 or more headache days per month, with at least 8 days of migraine⁴. The target population, chronic migraine was unchanged from the previous resubmissions. The proposed PBS restriction also specified that patients must also have experienced an inadequate response,

¹ Lipton R.B., Bigal M.E., Diamond M., et al. (2007), Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*, 68(5):343-9.

² Stovner L.J. & Andree C. (2010), Prevalence of headache in Europe: a review for the Eurolight project. *J Headache Pain*, 11(4):289-99.

³ Stark, R. J., Valenti, L., & Miller, G. C. (2007), Management of migraine in Australian general practice. *Medical Journal of Australia*, 187(3), 142-146. <https://doi.org/https://doi.org/10.5694/j.1326-5377.2007.tb01170.x>

⁴ In contrast, HFEM was defined as patients having an average 8 to 14 headache days per month (Table 1, Fremanezumab, PSD, November 2022 PBAC meeting).

intolerance or a contraindication to at least 3 prophylactic migraine medications. This was unchanged from the previous resubmissions.

- 4.4 The treatment options for acute migraines include simple analgesics such as non-narcotic analgesics, triptans and combination therapies such as any combination of triptans, ergot-derivatives, analgesics or simple analgesics with opiates.
- 4.5 Prophylactic treatment options for migraines include amitriptyline, candesartan, pizotifen, propranolol, sodium valproate, topiramate, and verapamil. Additional options for prophylactic chronic migraine treatment are PBS-listed CGRP medications, or botulinum toxin.
- 4.6 The resubmission's proposed clinical management algorithm placed erenumab alongside the other CGRP medications (galcanezumab, fremanezumab and eptinezumab) and botulinum toxin type A. The treatment algorithms did not consider the sequential use of CGRP medications.

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

5 Comparator

- 5.1 The resubmission nominated galcanezumab, fremanezumab and eptinezumab as the comparators to erenumab. The main arguments provided in support of this nomination were that galcanezumab, fremanezumab and eptinezumab were available on the PBS, for use in chronic migraine. Galcanezumab and fremanezumab were considered as the primary comparators, with eptinezumab considered a less relevant comparator due to the different mode of action. Although galcanezumab, fremanezumab and erenumab are CGRP receptor antagonists, galcanezumab and fremanezumab bind to the CGRP peptide, whereas erenumab blocks the CGRP receptor.
- 5.2 The evaluation considered that the proposed comparators were appropriate.
- 5.3 In the context of the cost-minimisation approach taken by the resubmission, a further consideration for the PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect. For the requested population, the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: galcanezumab, fremanezumab and eptinezumab.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (51), health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The PBAC also recalled the large number of consumer comments provided in relation to the July 2018 and March 2019 erenumab submissions. The comments from individuals currently being treated with erenumab described a range of benefits of treatment including the superior efficacy in comparison to other treatment options. Individuals stated that erenumab was associated with reduced migraine days and sensitivities (e.g. to light and noise), increased clarity and significant improvements in quality of life. Individuals stated that they experienced minimal adverse events. Individuals who wanted to access erenumab described the current high cost of private treatment. The comments also highlighted the need for additional effective treatment options for migraine. The health professional commented that erenumab was a highly effective treatment which was associated with mild adverse events.

6.3 The PBAC welcomed the advice received from Migraine Australia which described the aetiology of chronic migraine, the impact of chronic migraines on sufferers and the effects in terms of quality of life which was informed by a survey of over 500 of their community members. Migraine Australia provided detailed input regarding the current restrictions for CGRP medications on the PBS. The benefits of erenumab were described including that it is an effective preventative medication which reduced migraine attack frequency and severity. The PBAC specifically noted the advice relating to the benefits of erenumab treatment. The PBAC noted that this advice was supportive of the evidence provided in the submission.

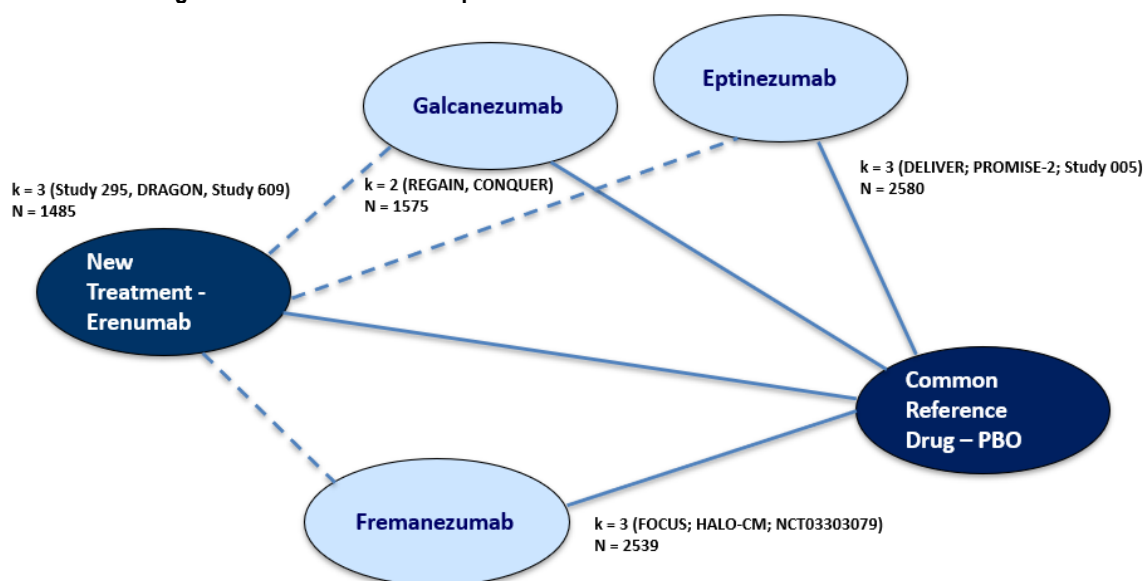
Clinical trials

6.4 The resubmission was based on 11 randomised controlled trials comparing:

- Erenumab (70 mg or 140 mg subcutaneous (SC) every 4 weeks) versus placebo: Study 295 (N=667); DRAGON (N=557); Study 609 (N=261).
- Galcanezumab (240 mg monthly SC or 120 mg monthly SC with a 240 mg loading dose) versus placebo: REGAIN (N=1113); CONQUER (N=462).
- Fremanezumab (675 mg quarterly or 225 mg monthly SC with a 675 mg loading dose) versus placebo: FOCUS (N=838); HALO-CM (N=1130); NCT03303079 (N=571).
- Eptinezumab (100 mg or 300 mg intravenous (IV) every 12 weeks) versus placebo: DELIVER (N=892); PROMISE-2 (N=1072); Study 005 (N=616).

- 6.5 The resubmission considered the DRAGON and Study 609 trials (erenumab) to be supplementary trials as (i) the DRAGON and Study 609 trials were solely conducted in Asian study sites to support the registration of erenumab 70 mg in China and Japan; (ii) the trials did not investigate the 140 mg dose; (iii) they did not provide an adequate subgroup of patients who had failed ≥ 3 prophylactic migraine medication categories; and (iv) Study 609 was conducted in a mixed population of chronic and episodic migraine.
- 6.6 The resubmission presented Study 255, an open-label extension of Study 295 (erenumab).
- 6.7 All trials have been previously considered by the PBAC, with the exception of DRAGON and Study 609.
- 6.8 The resubmission presented pre-specified subgroup analyses of patients with chronic migraine for all trials. The resubmission also presented *post-hoc* subgroup analyses of patients who had failed ≥ 3 prophylactic migraine medication categories (herein referred to as ≥ 3 treatment failures) from the erenumab Study 295 trial, the galcanezumab CONQUER and REGAIN trials and the eptinezumab DELIVER trial. This approach aligned with the listing of comparator treatments on the PBS, where *post-hoc* subgroup analysis data were used to support listing for a population with 3 or more treatment failures (paragraph 6.6, Galcanezumab PSD, July 2019 PBAC meeting; paragraph 6.5, Fremanezumab PSD, November 2019 meeting; paragraph 6.5, Eptinezumab PSD, July 2022 PBAC meeting).
- 6.9 The resubmission also presented meta-analyses for erenumab versus placebo for the whole trial populations and chronic migraine subgroups (erenumab, fremanezumab, galcanezumab, eptinezumab).
- 6.10 Finally, the resubmission presented indirect comparisons of:
- The whole trial populations for: one erenumab trial (Study 295); three fremanezumab trials (FOCUS, HALO-CM, NCT03303079); two galcanezumab trials (REGAIN, CONQUER); and three eptinezumab trials (DELIVER, PROMISE-2, Study 005) with placebo as the common comparator. Scenario analyses were also presented using the erenumab supplementary trials (DRAGON, Study 609).
 - *Post-hoc* subgroups of patients who had failed ≥ 3 prophylactic migraine medications for: one erenumab trial (Study 295); two galcanezumab trials (REGAIN, CONQUER); and one eptinezumab trial (DELIVER) with placebo as the common comparator.
- 6.11 Figure 1 presents a network diagram of the trials included to inform the indirect comparisons of erenumab with galcanezumab, fremanezumab and eptinezumab.

Figure 1: Network diagram of erenumab and comparators



Source: Constructed during the evaluation from Table 2.8, p43; Table 2.12, p52; Table A.3, pp139-140 of the resubmission. k = number of trials; n = number of patients enrolled; PBO = placebo.

6.12 Details of the trials presented in the resubmission are provided in Table 2.

Table 2: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Study 295 NCT02066415	Clinical study report: A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of AMG 334 in Chronic Migraine Prevention. Tepper S, Ashina M, Reuter U, Brandes J. L, Doležil D, Silberstein S, Winner P, Leonardi D, Mikol D, & Lenz R. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lipton R B, Tepper S J, Reuter U, Silberstein S, Stewart W F, Nilsen J, Leonardi D K, Desai P, Cheng S, Mikol D D et al. Erenumab in chronic migraine: patient-reported outcomes in a randomized double-blind study.	15 September 2016 <i>The Lancet Neurology</i> 2017;16(6):425-434 <i>Neurology</i> 2019 (19); e2250-e2260.
Study 609 NCT03812224	Clinical study report: A Phase 3 Japanese Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention. Takeshima T, Sakai F, Hirata K, Imai N, Matsumori Y, Yoshida R, Peng C, Cheng S, & Mikol D D. (2021). Erenumab treatment for migraine prevention in Japanese patients: Efficacy and safety results from a Phase 3, randomized, double-blind, placebo-controlled study. Hirata K, Takeshima T, Sakai F, Imai N, Matsumori Y, Tatsuoka Y, Numachi Y, Yoshida R, Peng C, Mikol D. D, Lima G P D S & Cheng S. Early onset of efficacy with erenumab for migraine prevention in Japanese patients: Analysis of two randomized, double-blind, placebo-controlled studies. Kitamura S, Takeshima T, Yui D, da Silva Lima G P, Koukakis R, Peng C, Yoshida R, Numachi Y & Hasebe M. Efficacy of Erenumab for Migraine Prevention in Japanese Patients with Episodic and Chronic Migraine: Results of a Post-Hoc Pooled Analysis.	17 February 2021 <i>Headache</i> 2021;61(6):927-935. <i>Brain and Behavior</i> 2022;12(3). <i>Neurology and Therapy</i> 2023;12(6):1993-2006.
DRAGON NCT03867201	Clinical study report: A 12-week phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of once monthly subcutaneous erenumab 70 mg in adult chronic migraine patients.	30 November 2021

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Trial ID	Protocol title/ Publication title	Publication citation
	Yu S, Kim B K, Wang H, Zhou J, Wan Q, Yu T, Lian Y, Arkuszewski M, Ecochard L, Wen S et al. A phase 3, randomised, placebo-controlled study of erenumab for the prevention of chronic migraine in patients from Asia: the DRAGON study.	<i>Journal of Headache and Pain</i> 2022;23(1):146.
Galcanezumab versus placebo		
CONQUER NCT03559257	<p>Ambrosini A., Estemalik E, Pascual J, Rettiganti M, Stroud C, Day K, & Ford J. Changes in acute headache medication use and health care resource utilization: Results from a randomized, double-blind, placebo-controlled clinical trial evaluating galcanezumab in adults with treatment-resistant migraine (CONQUER).</p> <p>Lipton R B, Buse D C, Sandoe C H, Ford J H, Hand A L, Jedynek J P, Port M D, & Detke H C. Changes in migraine interictal burden following treatment with galcanezumab: Results from a phase III randomized, placebo-controlled study.</p> <p>Mulleners W M, Kim B K, Láinez M J A, Lanteri-Minet M, Pozo-Rosich P, Wang S, Tockhorn-Heidenreich A, Aurora S K, Nichols R M, Yunes-Medina L, & Detke, H C. (2020). Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial.</p> <p>Tepper S J, Ailani J, Ford J H, Nichols R M, Li L Q, Kemmer P, Hand A L, & Tockhorn-Heidenreich A. Effects of Galcanezumab on Health-Related Quality of Life and Disability in Patients with Previous Failure of 2–4 Migraine Preventive Medication Categories: Results from a Phase IIIb Randomized, Placebo-Controlled, Multicenter Clinical Trial (CONQUER).</p>	<p><i>Journal of Managed Care and Specialty Pharmacy</i> 2022;28(6):645-656.</p> <p><i>Headache</i> 2023;63(5):683-691.</p> <p><i>The Lancet Neurology</i> 2020;19(10):814-825.</p> <p><i>Clinical Drug Investigation</i> 2022;42(3):263-275.</p>
REGAIN NCT02614261	<p>Detke H C, Goadsby P J, Wang S, Friedman D I, Selzler K J, & Aurora S K. (2018). Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study.</p> <p>Ruff D D, Ford J H, Tockhorn-Heidenreich A, Sexson M, Govindan S, Pearlman E M, Wang S J, Khan A. & Aurora S K. Efficacy of galcanezumab in patients with chronic migraine and a history of preventive treatment failure.</p> <p>Ford J, Tassorelli C, Leroux E, Wang S, Ayer D, Nichols R, & Detke H. Changes in patient functioning and disability: results from a phase 3, double-blind, randomized, placebo-controlled clinical trial evaluating galcanezumab for chronic migraine prevention (REGAIN).</p>	<p><i>Neurology</i> 2018; 91(24):e2211-e2221.</p> <p><i>Cephalalgia</i> 2019;39(8):931-944.</p> <p><i>Quality of Life Research</i> 2021;30(1):105-115.</p>
	Tobin J A, Joshi S, Ford J H, Nichols R M, Foster S A, Ruff D, Detke H C, & Aurora S K. Reductions in acute medication use and healthcare resource utilization in patients with chronic migraine: a secondary analysis of a phase 3, randomized, double-blind, placebo-controlled study of galcanezumab with open-label extension (REGAIN).	<i>Journal of Medical Economics</i> 2022;25(1):1030-1038.
Fremanezumab versus placebo		
FOCUS NCT03308968	Ashina M, Cohen J M, Galic M, Campos V R, Barash S, Ning X, Kessler Y, Janka L, & Diener H C. Efficacy and safety of fremanezumab in patients with episodic and chronic migraine with documented inadequate response to 2 to 4 classes of migraine preventive medications over 6 months of treatment in the phase 3b FOCUS study.	<i>Journal of Headache and Pain</i> 2021;22(1).
	Ferrari, M. D., Diener, H. C., Ning, X., Galic, M., Cohen, J. M., Yang, R., Mueller, M., Ahn, A. H., Schwartz, Y. C., Grozinski-Wolff, M., Janka, L., & Ashina, M. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial.	<i>The Lancet</i> 2019;394(10203):1030-1040.

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Trial ID	Protocol title/ Publication title	Publication citation
HALO-CM NCT02621931 ^g	Silberstein S D, Dodick D W, Bigal M E, Yeung P P, Goadsby PJ, Blankenbiller T, Grozinski-Wolff, M, Yang R, Ma Y, & Aycardi E. Fremanezumab for the preventive treatment of chronic migraine. Lipton R B, Cohen J M, Gandhi S K, Yang R, Yeung P P, & Buse D C. Effect of fremanezumab on quality of life and productivity in patients with chronic migraine.	<i>New England Journal of Medicine</i> 2017;377(22): 2113-2122. <i>Neurology</i> 2020;95(7):E878-E888.
NCT03303079 ^h	Sakai F, Suzuki N, Kim B K, Igarashi H, Hirata K, Takeshima T, Ning X, Shima T, Ishida M, Iba K et al. Efficacy and safety of fremanezumab for chronic migraine prevention: multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in Japanese and Korean patients. Imai, N., Isogai, Y., Shibasaki, Y., Nakai, M., Ishida, M., Ning, X., & Koga, N. Effects of Fremanezumab on Medication Overuse in Japanese Chronic Migraine Patients: Post Hoc Analysis of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial.	<i>Headache</i> 2021;61(7):1092-1101. <i>Neurology and Therapy</i> 2023;12(6):1981-1991.
Eptinezumab versus placebo		
DELIVER NCT04418765	Ashina M, Lanteri-Minet M, Pozo-Rosich P, Ettrup A, Christoffersen C L, Josiassen M K, Phul R, Sperling B. Safety and efficacy of eptinezumab for migraine prevention in patients with two-to-four previous preventive treatment failures (DELIVER): a multi-arm, randomised, double-blind, placebo-controlled, phase 3b trial.	<i>The Lancet Neurology</i> 2022;21(7):597-607.
PROMISE-2 NCT02974153	Lipton R B, Goadsby P J, Smith J, Schaeffler B A, Biondi D M, Hirman J, Pederson S, Allan B, Cady R. (2020). Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. Silberstein S, Diamond M, Hindiyeh N A, Biondi D M, Cady R, Hirman J, Allan B, Pederson S, Schaeffler B, Smith J. Eptinezumab for the prevention of chronic migraine: Efficacy and safety through 24 weeks of treatment in the phase 3 PROMISE-2 (Prevention of migraine via intravenous ALD403 safety and efficacy-2) study. Houts C R, McGinley J S, Wirth R J, Cady R, Lipton R B. (2021). Reliability and validity of the 6-item Headache Impact Test in chronic migraine from the PROMISE-2 study. Lipton R B, Goadsby P J, Dodick D W, McGinley J S, Houts C R, Wirth R J, Kymes S, Ettrup A, Østerberg O, Cady R, Ashina M, Buse D C. Evaluating the clinical utility of the patient-identified most bothersome symptom measure from PROMISE-2 for research in migraine prevention.	<i>Neurology</i> 2020;94(13):E1365-E1377. <i>Journal of Headache and Pain</i> 2020;21(1). <i>Quality of Life Research</i> 2021;30(3):931-943. <i>Headache</i> 2022;62(6):690-699.
Study 005 NCT02275117	Dodick D W, Lipton R B, Silberstein S, Goadsby P J, Biondi D, Hirman J, Cady R, Smith J. Eptinezumab for prevention of chronic migraine: A randomized phase 2b clinical trial	<i>Cephalalgia</i> 2019;39(9):1075-1085.

Source: Table 2.5, pp28-35 of the resubmission.

PBAC = Pharmaceutical Benefits Advisory Committee.

6.13 The key features of the direct randomised trials are summarised in Table 3.

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Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Subgroup of patients failed ≥ 3 prophylactic therapies
Erenumab vs placebo						
Study 295	677	R, DB, 12 weeks	Low	CM; included patients with no therapeutic response ≤3 prior prophylactic medication categories.	Change from baseline in MMDs; Responder: ≥ 50% reduction in MMDs.	Yes (post-hoc analyses)
DRAGON	557	R, DB, 12 weeks	Low	CM; included patients with no therapeutic response ≤3 prior prophylactic medication categories.	Change from baseline in MMDs; Responder: ≥ 50% reduction in MMDs.	No
Study 609	261	R, DB, 24 weeks	Low	CM and EM; included patients with no therapeutic response ≤3 prior prophylactic medication categories.	Change from baseline in MMDs; Responder: ≥ 50% reduction in MMDs.	No
Galcanezumab vs placebo						
REGAIN	1113	R, DB 3 months	Low	CM, included patients who failed ≤3 migraine preventive treatments from different classes.	Change from baseline in MHDs; Responder: ≥ 50% reduction in MMDs.	Yes (post-hoc analyses)
CONQUER	462	R, DB 3 months	Low	CM and EM, included patients who failed 2-4 preventive medication categories.	Change from baseline in MHDs; Responder: ≥ 50% reduction in MMDs.	Yes (post-hoc analyses)
Fremanezumab vs placebo						
FOCUS	838	R, DB 12 weeks	Low	CM and EM; included patients who failed 2-4 classes of preventive medications	Change from baseline in MMDs; Responder: ≥ 50% reduction in MMDs.	No published data ^a
HALO-CM	1130	R, DB 12 weeks	Low	CM, included patients who failed <2 classes of migraine preventive medications	Change from baseline in MHDs (of at least moderate severity) and MMDs; Responder: ≥ 50% reduction in MMDs.	N/A
NCT03303079	571	R, DB 12 weeks	Low	CM, included patients who have failed <2 classes of migraine preventive medications	Change from baseline in MHDs; Responder: ≥ 50% reduction in MMDs.	N/A
Eptinezumab vs placebo						
DELIVER	892	R, DB 24 weeks	Low	CM and EM, included patients who failed 2-4 preventative treatments	Change from baseline in MMDs; Responder: ≥ 50% reduction in MMDs.	Yes (post-hoc analyses)
PROMISE-2	1072	R, DB 12 weeks	Low	CM, no restriction on number of prior preventive treatments	Change from baseline in MMDs; Responder: ≥ 50% reduction in MMDs.	No
Study 005	616	R, DB 12 weeks	Unclear	CM, no restriction on number of prior preventive treatments	Responder: ≥ 75% reduction in MMDs; Change from baseline in MMDs.	No

Source: Constructed during the evaluation from Table 2.6, p37; p87; Table A.3, pp139-140 of the resubmission.

CM = Chronic migraine; DB = Double blind; EM = Episodic migraine; HIT-6 = Headache Impact Test-6; ICHD-3 = International Classification of Headache Disorders; MHDs = Monthly headache days; MIDAS=Migraine Disability Assessment; MMDs = Monthly migraine days; MSQ=Migraine-Specific Quality of Life Questionnaire; PGI-S=Patient Global Impression of Severity of Illness; PSD = Public summary document; R = Randomised; wks = weeks.

^a Redated data from Para. 6.5, Fremanezumab, PSD, November 2019 PBAC meeting.

- 6.14 The PBAC previously considered the erenumab Study 295 trial and the comparator trials to have a low risk of bias, with the exception of the eptinezumab Study 005 trial, which was determined to have an unclear risk of bias. The erenumab DRAGON and Study 609 trials were assessed as having an overall low risk of bias.
- 6.15 The resubmission acknowledged that the risk of bias was high when subgroups and/or *post-hoc* analyses were used as the primary analysis (e.g., by migraine subtype and/or preventive treatment failure subgroups). However, the subgroups reflected the proposed PBS population and the approach was consistent with that taken to support the listing of galcanezumab, fremanezumab and eptinezumab.
- 6.16 The resubmission did not conduct *post-hoc* subgroup analyses for the DRAGON and Study 609 trials given that they were considered supplementary trials and there were a limited number of patients included meeting these criteria. Only 6 and 14 patients treated with erenumab 70 mg in the DRAGON and Study 609 trials, respectively, in the *post hoc* subgroup (≥ 3 treatment failures).
- 6.17 There were multiple differences between the trials, including:
- Population/eligibility criteria:
 - Some trials included patients with episodic migraine.
 - The trials varied in terms of the number of prior prophylactic medication failures. In particular, the HALO-CM and NCT03303079 trials recruited patients who were less treatment-experienced.
 - Population/demographics:
 - The mean number of migraine days varied across the trials, with trials including only chronic migraine patients having a higher mean number of monthly migraine days (MMDs) at baseline (16-19 days) compared to trials including episodic and chronic migraine patients (12-14 days).
 - The proportion of patients receiving prior prophylactic medication varied across the trials depending on the eligibility criteria, with patients in the HALO-CM and NCT03303079 trials receiving less prior treatment.
 - Setting: Most trials were conducted across multi-regional sites, except the DRAGON and Study 609 trials (erenumab) and the NCT03303079 trial (fremanezumab), which were limited to Asian study sites. The impact of this difference was uncertain.
 - Duration of treatment: The double-blind treatment period was 12 weeks/ 3 months for most trials, except the Study 609 (erenumab) and DELIVER (eptinezumab) trials, which maintained double-blind treatment for 24 weeks. All the included trials reported outcomes at 12 weeks.
 - Outcome measures: The definition of a migraine also varied across the trials. The REGAIN and CONQUER trials (galcanezumab) defined a migraine day as a calendar

day with a headache lasting ≥ 30 minutes, compared to the other trials, where a migraine day comprised of a headache lasting ≥ 4 hours. This may bias the indirect comparison against galcanezumab if it is less effective against non-migraine headaches. In some trials, the use of medications (a triptan or ergot-derivative only, or any acute medication) on a calendar day was sufficient for a migraine day classification regardless of the duration of the symptoms (paragraph 6.9, Erenumab PSD, July 2018 PBAC meeting; paragraph 6.8 and Table 4, Eptinezumab PSD, July 2022 PBAC meeting).

- 6.18 The differences between the trials were partially mitigated using subgroup analyses. However, there remained considerable variation in placebo responses across the trials. The differences between the trials and placebo responses reduced the transitivity between the trials, increasing uncertainty in the results.
- 6.19 The resubmission proposed a non-inferiority margin for MMDs of 2 days in the interpretation of non-inferiority. The resubmission claimed that this was consistent with the interpretation of non-inferiority in previous migraine submissions (paragraph 6.15, Fremanezumab PSD, November 2019 PBAC meeting; paragraph 6.24, Atogepant PSD, July 2023 PBAC meeting).
- 6.20 The PBAC previously accepted that a change of 2 to 3 migraine or headache days per month was clinically meaningful or a minimally clinically important difference (MCID) (paragraph 7.9, Erenumab PSD, July 2018 PBAC meeting; paragraph 6.13, Fremanezumab PSD, November 2019 PBAC meeting; paragraph 6.16, Galcanezumab PSD, July 2019 PBAC meeting).
- 6.21 The resubmission also proposed an MCID of -2.3 change from baseline mean difference in the Headache Impact Test (HIT-6) score. A MCID of -2.3 change from baseline mean difference in the HIT-6 for chronic migraine, based on a study by Coeytaux (2006) was previously used in submissions for interpreting this endpoint (paragraph 6.25, Atogepant PSD, July 2023 PBAC meeting; paragraph 8, Botulinum toxin PSD, July 2012 PBAC meeting).

Comparative effectiveness

Erenumab versus placebo

- 6.22 Table 4 summarises the change from baseline in MMDs at 12 weeks/3 months across the erenumab trials.

Table 4: Results of the change from baseline in monthly migraine days at 12 weeks

Trial ID	ERE			Placebo			Mean difference	
	n/N (%)	Baseline mean (SD)	LSM change (SE / SD / 95% CI)	n/N (%)	Baseline mean (SD)	LSM change (SE / SD / 95% CI)	Difference in LSM (95% CI / SE)	p-value
Whole trial population - MMDs								
Erenumab 70 mg (12 weeks; except Study 609 (CM) 4-6 months)								
Study 295	178/188 (94.7)	17.94 (0.32)	-6.64 (-7.47, -5.81)	267/281 (95.0)	18.24 (0.28)	-4.18 (-4.86, -3.50)	-2.46 (-3.52, -1.39)	p<0.001
DRAGON	270/279 (96.8)	19.08 (5.27)	-8.19 (0.46)	274/278 (98.6)	19.34 (5.57)	-6.62 (0.45)	-1.57 (-2.83, -0.30)	p=0.015
Study 609	128/130 (98.5)	12.40 (0.53)	-3.61 (-4.46, -2.76)	128/131 (97.7)	11.84 (0.50)	-1.23 (-2.07, -0.39)	-2.38 (-3.43, -1.33)	p<0.001
Study 609 (CM) (4-6 months)	52/52 (100)	18.56 (3.96)	-5.11 (0.79)	50/50 (100)	17.72 (4.19)	-3.54 (0.81)	-1.57 (-3.39, 0.24)	p=0.089
Meta-analysis; all trials at Week 12; heterogeneity I ² = 0%, p = 0.52							-2.20 [-2.84, -1.55]	
Meta-analysis; trials at Week 12, excluding Study 609 (due to inclusion of EM patients); heterogeneity I ² = 10%, p = 0.29							-2.08 [-2.94, -1.22]	
Meta-analysis; trials of CM patients regardless of assessment timepoint; heterogeneity I ² = 0%, p = 0.50							-2.00 [-2.75, -1.26]	
Erenumab 140 mg (12 weeks)								
Study 295	182/187 (97.3)	17.78 (0.34)	-6.63 (-7.45, -5.80)	267/281 (95.0)	18.24 (0.28)	-4.18 (-4.86, -3.50)	-2.45 (-3.51, -1.38)	p<0.001
≥ 3 treatment failure post-hoc subgroup								
Study 295 (70 mg)	65/66 (98.5)	19.2 (4.21)	-5.38 (0.76)	96/98 (98)	18.6 (4.27)	-2.79 (0.60)	-2.59 (-4.48, -0.70)	p=0.0074
Study 295 (140 mg)	65/65 (100)	19.0 (4.69)	-7.0 (0.91)	96/98 (98)	18.6 (4.27)	-2.79 (0.60)	-4.21 (-6.34, -2.07)	p=0.0001

Source: Table 2.16, p67; Table 2.26, p84 of the resubmission.

CI = confidence interval; CM = Chronic Migraine; EM = episodic migraine; ERE = erenumab; LSM = least squares mean; MMDs = monthly migraine days; n = number of patients reporting data; N = total patients in arm; SD = standard deviation, SE = standard error.

Bold indicates statistically significant results

Blue shading indicates data previously considered by the PBAC.

- 6.23 In the Study 295 there was a statistically significant greater reduction in the change in MMDs from baseline to 12 weeks for erenumab 70 mg (-2.46; 95% CI: -3.52, -1.39; p<0.001) and erenumab 140 mg (-2.45; 95% CI: -3.51, -1.38; p<0.001) compared with placebo in patients with chronic migraine. The mean difference for both doses exceeded the MCID of 2 days.
- 6.24 The meta-analysis of erenumab trials found a statistically significant greater reduction in the change in MMDs from baseline to 12 weeks for erenumab 70 mg compared with placebo (-2.20; 95% CI: -2.84, -1.55). The mean difference exceeded the MCID of 2 days.
- 6.25 The *post-hoc* subgroup analysis of patients who had experienced ≥ 3 treatment failures found a similar mean reduction in the change in MMDs from baseline to 12 weeks for erenumab 70 mg versus placebo (-2.59; 95% CI: -4.48, -0.70; p<0.0074) and a higher mean reduction for erenumab 140 mg versus placebo (-4.21; 95% CI: -6.34, -2.07; p=0.0001) compared with the whole trial population.

6.26 Table 5 summarises the results for the proportion of patients achieving at least a 50% reduction in monthly migraine days across the included trials.

Table 5: Results of the proportion of patients achieving at least a 50% reduction in monthly migraine days

Trial ID	ERE n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)
Whole trial population			
Erenumab 70 mg (12 weeks)			
Study 295 ^b	75/188 (39.9)	66/281 (23.5)	2.18 (1.46, 3.27); p<0.001
DRAGON ^b	131/279 (47.0)	102/278 (36.7)	1.54 (1.09, 2.17); p=0.014
Study 609 (Week 12) ^{a,b}	46/130 (35.4)	18/131 (13.7)	3.53 (1.90, 6.57); p<0.001
Study 609 (Months 4-6) ^b	41/130 (31.5)	22/131 (16.8)	2.33 (1.29, 4.23); p=0.005
Meta-analysis; all trials at Week 12; heterogeneity I ² = 64%, p = 0.06			2.12 [1.39, 3.22]
Meta-analysis; all studies at longest follow-up; heterogeneity I ² = 13%, p = 0.32			1.85 [1.43, 2.40]
Meta-analysis; excluding Study 609 (due to inclusion of EM patients); heterogeneity I ² = 41%, p = 0.19			1.79 [1.27, 2.51]
Erenumab 140 mg (12 weeks)			
Study 295	77/187 (41.2)	66/281 (23.5)	2.34 (1.56, 3.51); p<0.001
≥ 3 treatment failure post-hoc subgroup			
Study 295 (70 mg)	23/66 (34.8)	15/98 (15.3)	2.96 (1.39, 6.27); p=0.0041
Study 295 (140 mg)	25/65 (38.5)	15/98 (15.3)	3.48 (1.64, 7.39); p=0.001

Source: Table 2.17, p69, and Table 2.27, p85 of the resubmission.

CI = confidence interval; EM = episodic migraine; ERE = erenumab; ITT = intention to treat; n = number of patients with event; N = total patients in arm; PBAC = Pharmaceutical Benefits Advisory Committee.

^a The ITT population of Study 609 comprised of patients with chronic migraine or episodic migraine; subgroup data for the chronic migraine population was not available for this endpoint.

^b Results were reported as adjusted odds ratio.

Bold indicates statistically significant results

Blue shading indicates data previously considered by the PBAC.

6.27 In the Study 295 trial there was a statistically significant higher proportion of patients that achieved a ≥ 50% reduction in MMDs from baseline to 12 weeks for erenumab 70 mg (adjusted odds ratio (OR)= 2.18; 95% CI: 1.46, 3.27; p<0.001) and erenumab 140 mg (OR=2.34; 95% CI: 1.56, 3.51; p<0.001) compared with placebo in patients with chronic migraine.

6.28 The meta-analysis of erenumab trials found there was a statistically significant higher proportion of patients achieving at least a 50% reduction in MMDs from baseline to 12 weeks for erenumab 70 mg compared with placebo (OR=2.12; 95% CI: 1.39, 3.22).

6.29 The *post-hoc* subgroup analysis of patients who had experienced ≥ 3 treatment failures found a higher proportion of patients achieving at least a 50% reduction in MMDs from baseline to 12 weeks for erenumab 70 mg versus placebo (OR=2.96; 95% CI: 1.39, 6.27; p<0.0041) and erenumab 140 mg versus placebo (OR=3.48; 95% CI: 1.64, 7.39; p=0.001) compared with the whole trial population.

6.30 Table 6 presents the results for the change in daily activity impact of headache from baseline, as measured by the HIT-6.

Table 6: Results for the change in daily activity impact of headache from baseline, as measured by the HIT-6

Trial ID	ERE ^a			Placebo			Mean difference	
	n/N (%)	Baseline mean (SD)	LSM change (SE / SD / 95% CI)	n/N (%)	Baseline mean (SD)	LSM change (SE / SD / 95% CI)	Difference in LSM (95% CI / SE)	p-value
Whole trial population (12 weeks)								
Erenumab 70 mg								
Study 295	180/188 (95.7)	63.4 (0.4)	-5.6 (-6.5, -4.6)	262/281 (93.2)	63.3 (0.3)	-3.1 (-3.9, -2.3)	-2.5 (-3.7, -1.2)	p<0.001
DRAGON	263/279 (94.3)	61.14 (6.28)	-7.43 (0.45)	268/278 (96.4)	61.31 (6.5)	-6.56 (0.45)	-0.87 (-2.13, 0.38)	p=0.172
Study 609 (Week 12) ^a	126/130 (96.9)	59.4 (0.5)	-5.6 (-6.7, -4.5)	124/131 (94.7)	59.6 (0.5)	-3.4 (-4.5, -2.3)	-2.2 (-3.6, -0.8)	p=0.002
Study 609 (Months 4-6) ^a	127/130 (97.7)	59.4 (0.5)	-6.0 (-6.9, -5.0)	125/131 (95.4)	59.6 (0.5)	-4.8 (-5.8, -3.9)	-1.1 (-2.3, 0.0)	p=0.060
Meta-analysis; all studies at Week 12; heterogeneity I ² = 47%, p = 0.15							-1.85 [-2.86, -0.84]	
Meta-analysis; all studies at longest follow-up; heterogeneity I ² = 49%, p = 0.14							-1.52 [-2.48, -0.57]	
Meta-analysis; excluding Study 609 (due to inclusion of EM patients); heterogeneity I ² = 71%, p = 0.06							-1.69 [-3.29, -0.10]	
Erenumab 140 mg								
Study 295	178/187 (95.2)	62.7 (0.4)	-5.6 (-6.5, -4.6)	262/281 (93.2)	63.3 (0.3)	-3.1 (-3.9, -2.3)	-2.5 (-3.7, -1.2)	p<0.001
≥ 3 treatment failure post-hoc subgroup								
Study 295 (Erenumab 70 mg)	63/66 (95.5)	NR	-5.06 (0.93)	95/98 (96.9)	NR	-1.51 (0.48)	-3.56 (-5.64, -1.47)	p=0.0009
Study 295 (Erenumab 140 mg)	64/65 (98.5)	NR	-5.14 (0.96)	95/98 (96.9)	NR	-1.51 (0.48)	-3.64 (-5.74, -1.53)	p=0.0008

Source: Table 2.19, p74, Table 2.40, p106 of the resubmission; pp320-321 of erenumab CSR. **Bold** indicates statistically significant results. CI = confidence interval; CM = chronic migraine; EM = Episodic Migraine; ERE = erenumab; HIT-6 = Headache Impact Test; ITT = intention to treat; LSM = least square means; N = number of patients in the analysis set; PBO = placebo, SD = standard deviation; SE = standard error

^a The ITT population of Study 609 comprised of patients with CM or EM; subgroup data for the CM subgroup was not available for this endpoint

- 6.31 In the Study 295 trial there was a statistically significant mean improvement in the HIT-6 total score from baseline to 12 weeks for erenumab 70 mg (-2.5; 95% CI: -3.7, -1.2; p<0.001) and erenumab 140 mg (-2.5; 95% CI: -3.7, -1.2; p<0.001) compared with placebo in patients with chronic migraine. The mean improvements in the HIT-6 total were greater than the MCID of -2.3.
- 6.32 The meta-analysis of erenumab trials found there was a statistically significant mean improvement in the HIT-6 total score from baseline to 12 weeks for erenumab 70 mg compared with placebo (-1.85; 95% CI: -2.86, -0.84).
- 6.33 The *post-hoc* subgroup analysis of patients who had experienced ≥ 3 treatment failures found a higher mean improvement in the HIT-6 total score from baseline to 12 weeks for erenumab 70 mg versus placebo (least squares mean (LSM) -3.56; 95% CI: -5.64, -1.47; p=0.0009) and erenumab 140 mg versus placebo (-3.64; 95% CI: -5.74, -1.53; p=0.0008) compared with the whole trial population.

ITCs: Erenumab versus galcanezumab, fremanezumab and eptinezumab

6.34 Table 7 presents the results for the indirect comparison of the change in MMDs, and Table 8 presents the results of the indirect treatment comparison of the number of patients experiencing a $\geq 50\%$ reduction in MMDs.

Table 7: Results of the indirect treatment comparison: Change from baseline in MMDs (whole trial populations/ chronic migraine pre-specified subgroup)

Comparison	Trial	Change from baseline in MMDs LSM (whole trial populations/CM subgroup)			Treatment effect: MD (95% CI); p-value
		ERE	Placebo	GAL/FREM/EPTI	
Erenumab 70 mg vs comparators					
Whole trial population (chronic migraine)					
ERE 70 mg vs PBO (12 weeks)	Study 295	-6.64 (-7.47, -5.81)	-4.18 (-4.86, -3.50)		-2.46 (-3.52, -1.39); p<0.001
Chronic migraine subgroup					
FREM 225 mg vs PBO (12 weeks) ^a	FOCUS (CM)		-0.7 (0.36)	-4.5 (0.36)	-3.8 (-4.8, -2.8); p<0.0001
	HALO-CM (CM)		-3.2 (0.4)	-5.0 (0.4)	-1.8 (-2.9, 0.7); p<0.001
	NCT03303079 (CM)		-2.8 (0.5)	-4.9 (0.5)	-2.1 (-3.10, -1.12); p<0.0001
	FOCUS, HALO-CM, NCT03303079 (I ² = 75%, p = 0.02)				-2.61 (-3.93, -1.28)
Indirect comparison erenumab 70 mg vs fremanezumab 225 mg monthly					0.15 [-1.55, 1.85] (p = 0.8627)
FREM 675 mg vs PBO (12 weeks)	FOCUS (CM)		-0.7 (0.36) ^a	-3.9 (0.36) ^a	-3.2 (-4.2, -2.2); p<0.0001
	HALO-CM (CM)		-3.2 (0.4)	-4.9 (0.4)	-1.7 (-2.8, -0.6); p<0.001
	NCT03303079 (CM)		-2.8 (0.5)	-4.1 (0.5)	-1.3 (-2.27, -0.29); p=0.011
	FOCUS, HALO-CM, NCT03303079 (I ² = 68%, p = 0.04)				-2.13 (-3.30, -0.95)
Indirect comparison erenumab 70 mg vs fremanezumab 675 mg quarterly					-0.33 [-1.916, 1.256] (p = 0.6834)
GAL 120 mg vs PBO (3 months)	REGAIN (CM)		-2.7 (0.4)	-4.8 (0.4)	-2.1 (-2.9, -1.3); p<0.001
	CONQUER (CM)		-2.2 (0.6)	-6.0 (0.7)	-3.7 (-5.2, -2.2); p<0.0001
	REGAIN, CONQUER (I ² = 60%, p = 0.12)				-2.79 (-4.43, -1.16)
Indirect erenumab 70 mg vs galcanezumab 120 mg					0.33 [-1.621, 2.281] (p = 0.7403)
Whole trial population					
EPTI 100 mg vs PBO (12 weeks)	DELIVER (CM/EM)		-2.1 (0.4)	-4.8 (0.4)	-2.7 (-3.4, -2.0); p<0.0001
	PROMISE-2 (CM)		-5.6 (NR)	-7.7 (NR)	-2.0 (-2.9, -1.2); p<0.0001
	Study 005 (CM)		-5.6 (6.6)	-7.7 (6.9)	-2.1 (-3.8, -0.4); p=0.018
	DELIVER, PROMISE-2, Study 005 (I ² = 0%, p = 0.51)				-2.41 (-2.91, -1.91)
Indirect comparison erenumab 70 mg vs eptinezumab 100 mg					-0.05 [-1.227, 1.127] (p = 0.9336)
Erenumab 140 mg vs comparators					
Whole trial population (chronic migraine)					
ERE 140 mg vs PBO (12 weeks)	Study 295	-6.63 (-7.45, -5.80)	-4.18 (-4.86, -3.50)		-2.45 (-3.51, -1.38); p<0.001
Chronic migraine subgroup					
FREM 225 mg vs PBO (12 weeks) ^a	FOCUS (CM)		-0.7 (0.36)	-4.5 (0.36)	-3.8 (-4.8, -2.8); p<0.0001
	HALO-CM (CM)		-3.2 (0.4)	-5.0 (0.4)	-1.8 (-2.9, -0.7); p<0.001
	NCT03303079 (CM)		-2.8 (0.5)	-4.9 (0.5)	-2.1 (-3.10, -1.12); p<0.001
	FOCUS, HALO-CM, NCT03303079 (I ² = 75%, p = 0.02)				-2.61 (-3.93, -1.28)
Indirect comparison erenumab 140 mg vs fremanezumab 225 mg monthly					0.16 [-1.54, 1.86] (p = 0.8536)
FREM 675 mg vs PBO (12 weeks)	FOCUS (CM)		-0.7 (0.36)	-3.9 (0.36)	-3.2 (-4.2, -2.2); p<0.0001
	HALO-CM (CM)		-3.2 (0.4)	-4.9 (0.4)	-1.7 (-2.8, -0.6); p<0.001
	NCT03303079 (CM)		-2.8 (0.5)	-4.1 (0.5)	-1.3 (-2.27, -0.29); p=0.011
	FOCUS, HALO-CM, NCT03303079 (I ² = 68%, p = 0.04)				-2.13 (-3.30, -0.95)

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Comparison	Trial	Change from baseline in MMDs LSM (whole trial populations/CM subgroup)			Treatment effect: MD (95% CI); p-value
		ERE	Placebo	GAL/FREM/EPTI	
Indirect comparison erenumab 140 mg vs fremanezumab 675 mg quarterly					
-0.32 [-1.906, 1.266] (p = 0.6925)					
GAL 120 mg vs PBO (3 months)	REGAIN (CM)		-2.7 (0.4)	-4.8 (0.4)	-2.1 (-2.9, -1.3); p<0.001
	CONQUER (CM)		-2.2 (0.6)	-6.0 (0.7)	-3.7 (-5.2, -2.2); p<0.0001
	REGAIN, CONQUER (I ² = 60%, p = 0.12)				-2.79 (-4.43, -1.16)
Indirect erenumab 140 mg vs galcanezumab 120 mg					
0.34 [-1.611, 2.291] (p = 0.7327)					
Whole trial population					
EPTI 100 mg vs PBO (12 weeks)	DELIVER (CM/EM)		-2.1 (0.4)	-4.8 (0.4)	-2.7 (-3.4, -2.0); p<0.0001
	PROMISE-2 (CM)		-5.6 (NR)	-7.7 (NR)	-2.0 (-2.9, -1.2); p<0.0001
	Study 005 (CM)		-5.6 (6.6)	-7.7 (6.9)	-2.1 (-3.8, -0.4); p=0.018
	DELIVER, PROMISE-2, Study 005 (I ² = 0%, p = 0.51)				-2.41 (-2.91, -1.91)
Indirect comparison erenumab 140 mg vs eptinezumab 100 mg					
-0.04 [-1.217, 1.137] (p = 0.9469)					

Source: Table 2.16, p67; Table 2.30, pp91-92; Table 2.40, p106; Table 2.42, p108; Table A.15, pp171-172; Figure A.1, p174 of the resubmission. **Blue shading** indicates data previously considered by the PBAC. There were slight variations in the results between the previously accepted PSDs compared to the resubmission, likely due to rounding (i.e., the PBAC PSDs have been truncated for publication).

CI = confidence intervals; CM = chronic migraine; EM = episodic migraine; ERE = erenumab; EPTI = eptinezumab; FREM = fremanezumab; GAL = galcanezumab; LSM = Least Square Means; MD = mean difference; MMDs = monthly migraine days; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; PBO = placebo; PSD = Public Summary Document.

^a With a 675 mg loading dose at baseline

Note: Indirect treatment comparison result <0 favours erenumab

Minor transcription / rounding errors corrected in NCT03303079, REGAIN, CONQUER and PROMISE-2.

Blue shading indicates data previously considered by the PBAC. There were slight variations in the results between the previously accepted PSDs compared to the resubmission, likely due to rounding (i.e., the PBAC PSDs have been truncated for publication).

Table 8: Results of the indirect treatment comparison: $\geq 50\%$ reduction in monthly migraine days (whole trial populations/pre-specified CM subgroup)

Comparison	Trial	$\geq 50\%$ reduction in monthly migraine days n/N (whole trial populations/CM subgroup)			Treatment effect: OR (95% CI); p-value
		ERE	Placebo	GAL/FREM/EPTI	
Erenumab 70 mg vs comparators					
Whole trial population (chronic migraine)					
ERE 70 mg vs PBO (12 weeks)	Study 295	75/188 (39.9%)	66/281 (23.5%)	-	2.18 (1.46, 3.27); p<0.001
Whole trial population (chronic and episodic migraine)					
FREM 225 mg vs PBO (12 weeks) ^a	FOCUS (CM/EM)	-	24/278 (8.6%)	97/283 (34.3%)	5.52 (3.40, 8.97)
	HALO-CM (CM) ^b	-	67/371 (18.1%)	153/371 (40.8%)	3.13 (2.24, 4.37)
	NCT03303079 (CM) ^b	-	25/190 (13.2%)	54/186 (29.0%)	2.70 (1.59, 4.57)
	FOCUS, HALO-CM, NCT03303079 ($I^2 = 58\%$, $p = 0.09$)				3.57 (2.41, 5.31)
Indirect comparison erenumab 70 mg vs fremanezumab 225 mg monthly					0.611 [0.347, 1.074] (p = 0.0867)
FREM 675 mg vs PBO (12 weeks)	FOCUS (CM/EM)	-	24/278 (8.6%)	95/276 (34.4%)	5.55 (3.41, 9.04)
	HALO-CM (CM) ^b	-	67/371 (18.1%)	141/375 (37.6%)	2.73 (1.95, 3.83)
	NCT03303079 (CM) ^b	-	25/190 (13.2%)	55/189 (29.1%)	2.71 (1.60, 4.58)
	FOCUS, HALO-CM, NCT03303079 ($I^2 = 47\%$, $p = 0.15$)				3.41 (2.17, 5.35)
Indirect comparison erenumab 70 mg vs fremanezumab 675 mg quarterly					0.639 [0.349, 1.171] (p = 0.1473)
Chronic migraine subgroup					
GAL 120 mg vs PBO (3 months)	REGAIN ^c	-	83/538 (15.4%)	75/273 (27.6%)	2.08 (1.46, 2.96)
	CONQUER ^{c,d}	-	9/98 (8.9%)	30/95 (32.0%)	4.56 (2.03, 10.27)
	REGAIN, CONQUER ($I^2 = 67\%$, $p = 0.08$)				2.82 (1.33, 6.00)
Indirect comparison erenumab 70 mg vs galcanezumab 120 mg					0.773 [0.329, 1.817] (p = 0.5549)
Whole trial population (chronic and episodic migraine)					
EPTI 100 mg vs PBO (12 weeks)	DELIVER (CM/EM)	-	39/298 (13.1%)	126/299 (42.1%)	4.84 (3.22, 7.27)
	PROMISE-2 (CM)	-	144/366 (39.3%)	205/356 (57.6%)	2.09 (1.56, 2.82)
	Study 005 (CM) ^h	-	47/116 (40.5%)	65/118 (55.1%)	1.80 (1.07, 3.02)
	DELIVER, PROMISE-2, Study 005 ($I^2 = 85\%$, $p = 0.002$)				2.65 (1.47, 4.76)
Indirect comparison erenumab 70 mg vs eptinezumab 100 mg					0.823 [0.403, 1.677] (p = 0.5912)
Whole trial population (chronic migraine)					
Erenumab 140 mg vs comparators					
ERE 140 mg vs PBO (12 weeks)	Study 295	77/187 (41.2%)	66/281 (23.5%)	-	2.34 (1.56, 3.51); p<0.001
Whole trial population (chronic and episodic migraine)					
FREM 225 mg vs PBO (12 weeks) ^a	FOCUS (CM/EM)	-	24/278 (8.6%)	97/283 (34.3%)	5.52 (3.40, 8.97)
	HALO-CM (CM) ^b	-	67/371 (18.1%)	153/371 (40.8%)	3.13 (2.24, 4.37)
	NCT03303079 (CM) ^b	-	25/190 (13.2%)	54/186 (29.0%)	2.70 (1.59, 4.57)
	FOCUS, HALO-CM, NCT03303079 ($I^2 = 58\%$, $p = 0.09$)				3.57 (2.41, 5.31)
Indirect comparison erenumab 140 mg vs fremanezumab 225 mg monthly					0.655 [0.372, 1.154] (p = 0.1436)
FREM 675 mg vs PBO (12 weeks)	FOCUS (CM/EM)	-	24/278 (8.6%)	95/276 (34.4%)	5.55 (3.41, 9.04)
	HALO-CM (CM) ^b	-	67/371 (18.1%)	141/375 (37.6%)	2.73 (1.95, 3.83)
	NCT03303079 (CM) ^b	-	25/190 (13.2%)	55/189 (29.1%)	2.71 (1.60, 4.58)
	FOCUS, HALO-CM, NCT03303079 ($I^2 = 47\%$, $p = 0.15$)				3.41 (2.17, 5.35)
Indirect comparison erenumab 140 mg vs fremanezumab 675 mg quarterly					0.686 [0.374, 1.259] (p = 0.2237)

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Comparison	Trial	≥ 50% reduction in monthly migraine days n/N (whole trial populations/CM subgroup)			Treatment effect: OR (95% CI); p-value
		ERE	Placebo	GAL/FREM/EPTI	
Chronic migraine subgroup					
GAL 120 mg vs PBO (3 months)	REGAIN ^c	-	83/538 (15.4%)	75/273 (27.6%)	2.08 (1.46, 2.96)
	CONQUER ^{c,d}	-	9/98 (8.9%)	30/95 (32.0%)	4.56 (2.03, 10.27)
	REGAIN, CONQUER (I ² = 67%, p = 0.08)				2.82 (1.33, 6.00)
Indirect erenumab 140 mg vs galcanezumab 120 mg					
					0.83 [0.353, 1.952] (p = 0.669)
Whole trial population (chronic and episodic migraine)					
EPTI 100 mg vs PBO (12 weeks)	DELIVER (CM/EM)	-	39/298 (13.1%)	126/299 (42.1%)	4.84 (3.22, 7.27)
	PROMISE-2 (CM)	-	144/366 (39.3%)	205/356 (57.6%)	2.09 (1.56, 2.82)
	Study 005 (CM) ^d	-	47/116 (40.5%)	65/118 (55.1%)	1.80 (1.07, 3.02)
	DELIVER, PROMISE-2, Study 005 (I ² = 85%, p = 0.002)				2.65 (1.47, 4.76)
Indirect comparison erenumab 140 mg vs eptinezumab 100 mg					
					0.883 [0.432, 1.803] (p = 0.7327)

Source: Constructed during the evaluation from Table 2.17, p69; Table 2.32, pp93-94; 2.40, p106; Table A.17, pp176-177 of the resubmission.

CI = confidence intervals; CM = chronic migraine; EM = episodic migraine; ERE = erenumab; EPTI = eptinezumab; FREM = fremanezumab; GAL = galcanezumab; OR = odds ratio; PBAC = Pharmaceutical Benefits Advisory Committee; PBO = placebo.

Note: Result >1 favours erenumab

^a With a 675 mg loading dose at baseline

^b Result presented for average no. of headache days per month for HALO-CM and average no. of headache days of moderate or higher severity for NCT03303079 (migraine days not reported)

^c Number of responders not reported; resubmission back-calculated from N and proportion responders

^d Results are for subgroup analyses by migraine type (i.e., CM subgroup)

Bold indicates statistically significant result.

Blue shading indicates data previously considered by the PBAC.

- 6.35 The erenumab results were based on the whole trial population (i.e. all patients had chronic migraine) while the fremanezumab and galcanezumab results were based on the pre-specified chronic migraine subgroups. The smaller sample size in the subgroups increased the likelihood of not finding a statistically significant difference in the treatment effect.
- 6.36 The resubmission claimed that there were no statistically significant differences in the reduction in mean monthly migraine days between erenumab 70 mg or 140 mg and the comparators (fremanezumab 225 mg/675 mg, galcanezumab 120 mg, and eptinezumab 100 mg). The resubmission claimed that in the analyses versus fremanezumab and eptinezumab, the upper 95% CI was less than the non-inferiority margin of 2 days, supporting the non-inferiority of erenumab against these interventions. However, in the analyses against galcanezumab, the upper 95% CI exceeded the non-inferiority margin of 2 days.
- 6.37 The resubmission claimed that there were no statistically significant differences in terms of the proportion of patients achieving ≥ 50% reduction in monthly migraine days between erenumab 70 mg or 140 mg and the comparators (fremanezumab 225 mg/675 mg, galcanezumab 120 mg, and eptinezumab 100 mg).
- 6.38 There were multiple differences between the trials and there was a considerable variation in placebo responses across the trials in erenumab 70 mg, fremanezumab

HALO-CM, NCT03303079 and REGAIN. These differences reduced the transitivity between the trials, increasing uncertainty in the results (see paragraph 6.17).

- 6.39 Table 9 presents the indirect treatment comparisons of the change in baseline monthly migraine days and Table 10 presents the indirect comparisons of the $\geq 50\%$ reduction in monthly migraine days in the ≥ 3 treatment failure *post-hoc* subgroup. No indirect comparison of erenumab to fremanezumab was presented in the resubmission due to a lack of data on the fremanezumab *post-hoc* subgroup experiencing ≥ 3 treatment failures.

Table 9: Results of the indirect treatment comparison: Change from baseline in MMDs (≥ 3 TF post-hoc subgroup)

Comparison	Trial	Change from baseline in MMDs LSM (SE) (≥ 3 TF subgroup)			Treatment effect: LSM (95% CI)
		ERE	Placebo	GAL/FREM/EPTI	
ERE 70 mg vs GAL 120 mg					
ERE vs PBO	Study 295 (CM)	N=66 -5.38 (0.76)	N=98 -2.79 (0.60)	-	-2.59 (-4.48, -0.70) p=0.0074
GAL vs PBO	CONQUER (CM) ^a	-	N=42 -1.56 (NR)	N=42 -6.70 (NR)	-5.14 (1.30); p\leq0.001
	REGAIN (CM) ^b	-	N=103 -0.39 (0.76)	N=36 -5.64 (0.97)	-5.2 (-7.7, -2.8) ^c
Meta-analysis	CONQUER (subgroup), REGAIN (subgroup) $I^2 = 0\%$, $p = 0.95$				-5.20 (-6.95, -3.45)
Indirect estimate of effect MD [95% CI]; p-value; Result <0 favours erenumab					
Erenumab 70 mg, 12 weeks (Study 295) vs galcanezumab 120 mg, 3 months (CONQUER / REGAIN)					2.61 [0.034, 5.186] (p = 0.047)
ERE 70 mg vs EPTI 100 mg					
ERE vs PBO	Study 295 (CM)	N=66 5.38 (0.76)	N=98 -2.79 (0.60)	-	-2.59 (-4.48, -0.70) p=0.0074
EPTI vs PBO	DELIVER (CM/EM)	-	N=56 -1.7 (7.4)	N=56 -6.1 (7.3)	-4.4 (-7.15, -1.65) ^c
Indirect estimate of effect MD [95% CI]; p-value; Result <0 favours erenumab					
Erenumab 70 mg, 12 weeks (Study 295) vs eptinezumab 100 mg, 24 weeks (DELIVER)					1.81 [-1.527, 5.147] (p = 0.2877)
ERE 140 mg vs GAL 120 mg					
ERE vs PBO	Study 295 (CM)	N=65 -7.0 (0.91)	N=98 -2.79 (0.60)	-	-4.21 (-6.34, -2.07) p=0.0001
GAL vs PBO	CONQUER (CM) ^a	-	N=42 -1.56 (NR)	N=42 -6.70 (NR)	-5.14 (1.30); p\leq0.001
	REGAIN (CM) ^b	-	N=103 -0.39 (0.76)	N=36 -5.64 (0.97)	-5.2 (-7.7, -2.8) ^c
Meta-analysis	CONQUER (subgroup), REGAIN (subgroup) $I^2 = 0\%$, $p = 0.95$				-5.20 (-6.95, -3.45)
Indirect estimate of effect MD [95% CI]; p-value; Result <0 favours erenumab					
Erenumab 140 mg, 12 weeks (Study 295) vs galcanezumab 120 mg, 3 months (CONQUER / REGAIN)					0.99 [-1.771, 3.751] (p = 0.4821)
ERE 140 mg vs EPTI 100 mg					
ERE vs PBO	Study 295 (CM)	N=65 -7.0 (0.91)	N=98 -2.79 (0.60)	-	-4.21 (-6.34, -2.07) p=0.0001
EPTI vs PBO	DELIVER (CM/EM)	-	N=56 -1.7 (7.4)	N=56 -6.1 (7.3)	-4.4 (-7.15, -1.65) ^c
Indirect estimate of effect MD [95% CI]; p-value; Result <0 favours erenumab					
Erenumab 140 mg, 12 weeks (Study 295) vs eptinezumab 100 mg, 24 weeks (DELIVER)					0.19 [-3.291, 3.671] (p = 0.9148)

Source: Table 2.25, p83; Table 2.26, p84; Table 2.27, p85; Table 2.30, pp91-92; Table 2.31, p92; Table 2.32, pp93-94; Table 2.33, p94; Table 2.40, p106; Table A.16, p173 of the resubmission. **Bold** indicates statistically significant result.

CI = confidence interval; CM = chronic migraine; EM = episodic migraine; EPTI = eptinezumab; ERE = erenumab; FREM = fremanezumab; GAL = galcanezumab; LSM = least squares mean; MD = mean difference; MMDs = monthly migraine days; N = number of patients in the subgroup; NR = not reported; PBAC = Pharmaceutical Benefits Advisory Committee; PBO = placebo; SD = standard deviation; SE = standard error; TF = treatment failure.

^a The CONQUER trial reports outcomes for the CM subgroup of patients with 3-4 prior preventive medication category failures.

^b The REGAIN trial reports outcomes for the subgroup of patients with 3 preventive medication failures (not necessarily 3 classes of medications).

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^c LSM difference and/or 95% CI not reported in study report. Difference and/or 95% CI in mean change calculated in RevMan/Study reported proportion only; n back-calculated.

Blue shading indicates data previously considered by the PBAC.

Table 10: Results of the indirect treatment comparison: $\geq 50\%$ reduction in monthly migraine days (≥ 3 TF post-hoc subgroup)

Comparison	Trial	$\geq 50\%$ reduction in monthly migraine days, n/N (%) (≥ 3 TF subgroup)			Treatment effect: OR (95% CI)
		ERE	Placebo	GAL/FREM/EPTI	
ERE 70 mg vs GAL 120 mg					
ERE vs PBO	Study 295 (CM)	23/66 (34.8)	15/98 (15.3)		2.96 (1.39, 6.27); p=0.0041
GAL vs PBO	CONQUER (CM) ^a	-	4/42 (8.4)	17/42 (41.5)	6.46 (1.94, 21.46)
	REGAIN (CM) ^b	-	6/103 (6.1)	10/36 (29.1)	6.22 (2.07, 18.69)
Meta-analysis	CONQUER (CM subgroup), REGAIN (CM subgroup) ($I^2 = 0\%$, $p = 0.45$)				6.33 (2.81, 14.24)
Indirect estimate of effect OR [95% CI]; p-value; Result >1 favours erenumab					
Erenumab 70 mg, 12 weeks (Study 295) vs galcanezumab 120 mg, 3 months (CONQUER / REGAIN)					0.468 [0.155, 1.415] ($p = 0.1784$)
ERE 70 mg vs EPTI 100 mg					
ERE vs PBO	Study 295 (CM)	23/66 (34.8)	15/98 (15.3)	-	2.96 (1.39, 6.27); p=0.0041
EPTI vs PBO	DELIVER (CM/EM)	-	5/56 (8.9)	17/56 (30.4)	4.45 (1.51, 13.10)
Indirect estimate of effect OR [95% CI]; p-value; Result >1 favours erenumab					
Erenumab 70 mg, 12 weeks (Study 295) vs eptinezumab 100 mg, 12 weeks (DELIVER)					0.665 [0.178, 2.482] ($p = 0.544$)
ERE 140 mg vs GAL 120 mg					
ERE vs PBO	Study 295 (CM)	25/65 (38.5)	15/98 (15.3)	-	3.48 (1.64, 7.39); p=0.001
GAL vs PBO	CONQUER (CM) ^a	-	4/42 (8.4)	17/42 (41.5)	6.46 (1.94, 21.46)
	REGAIN (CM) ^b	-	6/103 (6.1)	10/36 (29.1)	6.22 (2.07, 18.69)
Meta-analysis	CONQUER (subgroup), REGAIN (subgroup) ($I^2 = 0\%$, $p = 0.45$)				6.33 (2.81, 14.24)
Indirect estimate of effect OR [95% CI]; p-value; Result >1 favours erenumab					
Erenumab 140 mg, 12 weeks (Study 295) vs galcanezumab 120 mg, 3 months (CONQUER / REGAIN)					0.55 [0.182, 1.663] ($p = 0.2894$)
ERE 140 mg vs EPTI 100 mg					
ERE vs PBO	Study 295 (CM)	25/65 (38.5)	15/98 (15.3)	-	3.48 (1.64, 7.39); p=0.001
EPTI vs PBO	DELIVER (CM/EM)	-	5/56 (8.9)	17/56 (30.4)	4.45 (1.51, 13.10)
Indirect estimate of effect OR [95% CI]; p-value; Result >1 favours erenumab					
Erenumab 140 mg, 12 weeks (Study 295) vs eptinezumab 100 mg, 12 weeks (DELIVER)					0.782 [0.21, 2.918] ($p = 0.7144$)

Source: Table 2.25, p83; Table 2.26, p84; Table 2.27, p85; Table 2.30, pp91-92; Table 2.31, p92; Table 2.32, pp93-94; Table 2.33, p94; Table 2.40, p106; Table A.16, p173 of the resubmission.

CI = confidence interval; CM = chronic migraine; EM = episodic migraine; EPTI = eptinezumab; ERE = erenumab; FREM = fremanezumab; GAL = galcanezumab; LSM = least squares mean; N = number of patients in the subgroup; NR = not reported; OR = odds ratio; PBAC = Pharmaceutical Benefits Advisory Committee; PBO = placebo; SD = standard deviation; SE = standard error; TF = treatment failure.

^a The CONQUER trial reports outcomes for the CM subgroup of patients with 3-4 prior preventive medication category failures.

^b The REGAIN trial reports outcomes for the subgroup of patients with 3 preventive medication failures (not necessarily 3 classes of medications).

Blue shading indicates data previously considered by the PBAC.

6.40 The resubmission claimed that there were no statistically significant differences in the change in baseline monthly migraine days in the ≥ 3 treatment failure subgroup, except for erenumab 70 mg versus galcanezumab. The comparison of erenumab 70 mg versus galcanezumab was statistically significant ($p = 0.047$), in favour of

galcanezumab. Furthermore, the upper 95% CI exceeded the non-inferiority margin of 2 days in all the indirect comparisons.

- 6.41 The resubmission claimed that there were no statistically significant differences in the proportion of responders in the ≥ 3 treatment failure *post-hoc* subgroup.
- 6.42 There were multiple differences between the trials and there was a considerable variation in placebo responses across the erenumab 70 mg, fremanezumab HALO-CM, NCT03303079 and REGAIN trials (refer to paragraphs 6.17 and 6.18). These differences reduced the transitivity between the trials, increasing uncertainty in the results. Furthermore, the *post hoc* subgroup analyses reduced the sample sizes, increasing the likelihood of not finding statistically significant differences in the treatment effect.

Comparative harms

- 6.43 Table 11 presents a summary of the adverse events (AEs) for the erenumab trials.

Table 11: Summary of key adverse events in the erenumab trials

Trial ID	ERE n/N (%)	Placebo n/N (%)	RR/OR (95% CI) ^a	RD (95% CI) ^a
TEAEs				
Erenumab 70 mg (12-24 weeks)				
Study 295 (CM)	83/190 (43.7)	110/282 (39.0)	1.12 (0.90, 1.39)	0.05 (-0.04, 0.14)
DRAGON (CM)	127/279 (45.5)	132/278 (47.5)	0.96 (0.80, 1.15)	-0.02 (-0.10, 0.06)
Study 609 (CM/EM)	86/130 (66.2)	78/131 (59.5)	1.11 (0.92, 1.34)	0.07 (-0.05, 0.18)
Erenumab 140 mg (12-24 weeks)				
Study 295 (CM)	88/188 (46.8)	110/282 (39.0)	1.20 (0.97, 1.48)	0.08 (-0.01, 0.17)
Any Grade 3+ treatment-emergent AEs				
Erenumab 70 mg (12-24 weeks)				
Study 295 (CM)	11/190 (5.8)	13/282 (4.6)	1.26 (0.57, 2.74)	0.01 (-0.03, 0.05)
DRAGON (CM)	9/279 (3.2)	14/278 (4.7)	0.64 (0.28, 1.46)	-0.02 (-0.05, 0.01)
Study 609 (CM/EM)	4/130 (3.1)	2/131 (1.5)	2.02 (0.38, 10.81)	0.02 (-0.02, 0.05)
Erenumab 140 mg (12-24 weeks)				
Study 295 (CM)	4/188 (2.1)	13/282 (4.6)	0.46 (0.15, 1.39)	-0.02 (-0.06, 0.01)
Any Serious AE				
Erenumab 70 mg (12-24 weeks)				
Study 295 (CM)	6/190 (3.2)	7/282 (2.5)	1.27 (0.43, 3.73)	0.01 (-0.02, 0.04)
DRAGON (CM)	7/279 (2.5)	7/278 (2.5)	1.00 (0.35, 2.80)	0.00 (-0.03, 0.03)
Study 609 (CM/EM)	2/130 (1.5)	2/131 (1.5)	1.01 (0.14, 7.05)	0.00 (-0.03, 0.03)
Erenumab 140 mg (12-24 weeks)				
Study 295 (CM)	2/188 (1.1)	7/282 (2.5)	0.43 (0.09, 2.04)	-0.01 (-0.04, 0.01)
Any TEAE leading to discontinuation				
Erenumab 70 mg (12-24 weeks)				
Study 295 (CM)	0/190 (0)	2/282 (0.7)	0.30 (0.01, 6.14)	-0.01 (-0.02, 0.00)
DRAGON (CM)	2/279 (0.7)	2/278 (0.7)	1.00 (0.14, 7.02)	0.00 (-0.01, 0.01)
Study 609 (CM/EM)	0/130 (0)	0/131 (0)	NE	0.00 (0.00, 0.00)
Erenumab 140 mg (12-24 weeks)				
Study 295 (CM)	2/188 (1.1)	2/282 (0.7)	1.50 (0.21, 10.56)	0.00 (-0.01, 0.02)
Deaths				
Erenumab 70 mg (12-24 weeks)				
Study 295 (CM)	0/190 (0)	0/282 (0)	NE	0.00 (0.00, 0.00)
DRAGON (CM)	0/279 (0)	0/278 (0)	NE	0.00 (0.00, 0.00)
Study 609 (CM/EM)	0/130 (0)	0/131 (0)	NE	0.00 (0.00, 0.00)
Erenumab 140 mg (12-24 weeks)				
Study 295 (CM)	0/188 (0)	0/282 (0)	NE	0.00 (0.00, 0.00)

Source: Table 2.20, p77 of the resubmission.

AE = adverse event; CI = confidence interval; CM = chronic migraine; EM = episodic migraine; ERE = erenumab; n = number of patients reporting data; N = total patients in arm; NA = not applicable; NE = not estimable; NR = not reported; OR = odds ratio; PBAC = Pharmaceutical Benefits Advisory Committee; PBO = placebo; RR = risk ratio; RD = risk difference; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Notes: Study 295 (CM) and DRAGON (CM) were 12 weeks; Study 609 (CM/EM) was 24 weeks; Treatment differences were calculated post-hoc for the purposes of the submission.

Blue shading indicates data previously considered by the PBAC.

6.44 In the Study 295 trial, the proportion of patients experiencing any treatment-emergent AEs was 46.8%, 43.7%, and 39.0% in the erenumab 140 mg arm, erenumab 70 mg and placebo arms, respectively. Serious AEs occurred in 1.1%, 3.2% and 2.5% of patients in the erenumab 140 mg, erenumab 70 mg and placebo arms, respectively. The resubmission claimed that there was no apparent dose relationship in the proportion of patients with Grade 3 or higher AEs or serious AEs between the erenumab 140 mg and 70 mg arms. The resubmission also claimed that the incidence

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of AEs resulting in discontinuation was low ($\leq 1\%$), indicating that AEs were manageable, and no fatal AEs were reported during the study.

6.45 Of the most frequently reported events, injection site pain, upper respiratory tract infection, constipation, muscle spasms and migraine, were reported more frequently in the erenumab 70 mg and/or erenumab 140 mg arms than in the placebo arm, with the only significant differences occurring in the rates of constipation (4.3% versus 0.4%) and injection site erythema (3.2% versus 0%) between erenumab 140 mg and placebo.

6.46 Table 12 presents the indirect comparisons of key AEs.

Table 12: Results of the indirect treatment comparison: safety outcomes (whole trial populations)

Comparison	Trial ID	At least one AE n/N (%) (whole trial populations)			Treatment effect: RR (95% CI)
		ERE	Placebo	GAL/FREM/EPTI	
At least one AE					
ERE 140 mg	Study 295	88/188 (46.8)	110/282 (39.0)	-	1.20 (0.97, 1.48)
ERE 70 mg	Study 295, DRAGON, Study 609	296/599 (49.4)	320/691 (46.3)	-	1.05 (0.94, 1.17)
GAL 120 mg	REGAIN, CONQUER	-	401/788 (50.9)	278/505 (55.0)	1.07 (0.89, 1.28)
FREM 225/675mg	FOCUS, HALO-CM, NCT03303079	-	984/1686 (58.4)	1047/1694 (61.8)	1.06 (1.01, 1.13)
EPTI 100 mg	DELIVER, PROMISE-2, Study 005	-	358/785 (45.6)	352/777 (45.3)	0.99 (0.89, 1.11)
Erenumab vs comparators; indirect treatment comparison				Indirect estimate of effect RR [95% CI]; p-value Result <1 favours erenumab	
Erenumab 70 mg vs galcanezumab 120 mg				0.981 [0.794, 1.213] (p = 0.8616)	
Erenumab 70 mg vs fremanezumab 225 mg/675 mg				0.991 [0.876, 1.12] (p = 0.8799)	
Erenumab 70 mg vs eptinezumab 100 mg				1.061 [0.908, 1.239] (p = 0.4583)	
Erenumab 140 mg vs galcanezumab 120 mg				1.121 [0.849, 1.482] (p = 0.4199)	
Erenumab 140 mg vs fremanezumab 225 mg/675 mg				1.132 [0.91, 1.409] (p = 0.266)	
Erenumab 140 mg vs eptinezumab 100 mg				1.212 [0.955, 1.538] (p = 0.1137)	
Comparison	Trial ID	Serious AEs (whole trial populations)			Treatment effect: RR (95% CI)
		Erenumab	Placebo	GAL/FREM/EPTI	
Serious AEs					
ERE 140 mg	Study 295	2/188 (1.1)	7/282 (2.5)	-	0.43 (0.09, 2.04)
ERE 70 mg	Study 295, DRAGON, Study 609	15/599 (2.5)	16/691 (2.3)	-	1.11 (0.55, 2.22)
GAL 120 mg	REGAIN, CONQUER	-	6/788 (0.8)	3/505 (0.6)	0.74 (0.17, 3.17)
FREM 225/675mg	FOCUS, HALO-CM, NCT03303079	-	22/1686 (1.3)	18/1694 (1.1)	0.80 (0.42, 1.52)
EPTI 100 mg	DELIVER, PROMISE-2, Study 005	-	8/785 (1.0)	16/1127 (1.4)	1.48 (0.62, 3.49)
Erenumab vs comparators; indirect treatment comparison				Indirect estimate of effect RR [95% CI]; p-value Result <1 favours erenumab	
Erenumab 70 mg vs galcanezumab 120 mg				1.5 [0.297, 7.585] (p = 0.6239)	
Erenumab 70 mg vs fremanezumab 225 mg/675 mg				1.388 [0.537, 3.584] (p = 0.4987)	
Erenumab 70 mg vs eptinezumab 100 mg				0.75 [0.247, 2.277] (p = 0.6116)	
Erenumab 140 mg vs galcanezumab 120 mg				0.581 [0.068, 4.933] (p = 0.6189)	
Erenumab 140 mg vs fremanezumab 225 mg/675 mg				0.538 [0.099, 2.906] (p = 0.4709)	
Erenumab 140 mg vs eptinezumab 100 mg				0.291 [0.049, 1.729] (p = 0.1744)	

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Comparison	Trial ID	AEs resulting in discontinuation n/N (%) (whole trial populations)			Treatment effect: RR (95% CI)
		Erenumab	Placebo	GAL/FREM/EPTI	
AEs resulting in discontinuation					
ERE 140 mg	Study 295	2/188 (1.1)	2/282 (0.7)	-	1.50 (0.21, 10.56)
ERE 70 mg	Study 295, DRAGON, Study 609	2/599 (0.3)	4/691 (0.6)	-	0.70 (0.14, 3.60)
GAL 120 mg	REGAIN, CONQUER	-	6/788 (0.8)	2/505 (0.4)	0.71 (0.10, 5.34)
FREM 225/675mg	FOCUS, HALO-CM, NCT03303079	-	26/1686 (1.5)	17/1694 (1.0)	0.69 (0.38, 1.28)
EPTI 100 mg	DELIVER, PROMISE-2, Study 005	-	3/785 (0.4)	6/777 (0.8)	1.75 (0.46, 6.71)
Erenumab vs comparators; indirect treatment comparison				Indirect estimate of effect RR [95% CI]; p-value Result <1 favours erenumab	
Erenumab 70 mg vs galcanezumab 120 mg				0.986 [0.076, 12.848] (p = 0.9914)	
Erenumab 70 mg vs fremanezumab 225 mg/675 mg				1.014 [0.179, 5.742] (p = 0.987)	
Erenumab 70 mg vs eptinezumab 100 mg				0.4 [0.049, 3.283] (p = 0.3936)	
Erenumab 140 mg vs galcanezumab 120 mg				2.113 [0.13, 34.45] (p = 0.5995)	
Erenumab 140 mg vs fremanezumab 225 mg/675 mg				2.174 [0.28, 16.9] (p = 0.458)	
Erenumab 140 mg vs eptinezumab 100 mg				0.857 [0.08, 9.2] (p = 0.8987)	

Source: Table 2.34, pp95-96 of the resubmission.

AE= adverse event; CI = confidence interval; EPTI = eptinezumab; ERE = erenumab; FREM = fremanezumab; GAL =galcanezumab; n = number of patients with event; N = total patients in arm; PBAC = Pharmaceutical Benefits Advisory Committee; RR = risk ratio.

Blue shading indicates data previously considered by the PBAC.

6.47 Overall, the risk of adverse events across the pivotal trials (Study 295, FOCUS, REGAIN, DELIVER) were similar; however, as trials were not powered to identify differences in safety the indirect comparisons were highly uncertain. The most reported events were injection site pain for erenumab, galcanezumab and fremanezumab, and nasopharyngitis for eptinezumab.

Benefits/harms

6.48 A benefits and harms table was not presented as the resubmission made a claim of non-inferiority.

Clinical claim

6.49 The resubmission described erenumab as non-inferior in terms of effectiveness compared to galcanezumab, fremanezumab and eptinezumab. On balance, the evaluation considered that this claim, although uncertain, was reasonably supported by the clinical evidence. Several issues increased uncertainty in the results:

- No head-to-head clinical trials comparing erenumab to the comparators were presented.
- The resubmission presented a series of indirect comparisons using placebo as the common comparator, including whole trial populations, pre-specified subgroup analyses (patients with chronic migraine) and *post-hoc* subgroup analyses (patients experiencing ≥ 3 treatment failures). There were multiple differences between the trials and there was considerable variation in placebo responses

across the trials. These differences reduced the transitivity between the trials, increasing uncertainty in the results.

- The use of subgroup analyses reduced the sample sizes and increased the likelihood of not finding a statistically significant difference in the treatment effect.
- There was no statistically significant difference in the reduction in the mean monthly migraine days between erenumab 70 mg or 140 mg and the comparators (fremanezumab 225 mg/675 mg, galcanezumab 120 mg, eptinezumab 100 mg) in the indirect comparisons using the chronic migraine populations. These analyses comparing erenumab to fremanezumab and eptinezumab reported that the upper 95% CI was less than the non-inferiority margin of 2 days, supporting the non-inferiority of erenumab against these interventions. However, in the analyses against galcanezumab, the upper 95% CI exceeded the non-inferiority margin of 2 days. This suggests that erenumab may be inferior to galcanezumab in terms of the reduction in monthly migraine days.
- There were no statistically significant differences in the reduction in the mean monthly migraine days between erenumab 70 mg or 140 mg and the comparators (galcanezumab 120 mg, eptinezumab 100 mg) in the indirect comparisons using the ≥ 3 treatment failure subgroup, except for the erenumab 70 mg versus galcanezumab. The comparison of erenumab 70 mg versus galcanezumab was statistically significant ($p = 0.047$), in favour of galcanezumab. Furthermore, the upper 95% CI exceeded the non-inferiority margin of 2 days in all the indirect comparisons. This suggests that erenumab may be inferior to galcanezumab in terms of the reduction in monthly migraine days. No indirect comparison of erenumab to fremanezumab was presented due to a lack of data on the subgroup experiencing ≥ 3 treatment failures.

6.50 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.51 The resubmission described erenumab as non-inferior in terms of safety compared to galcanezumab, fremanezumab and eptinezumab.

6.52 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.53 The resubmission presented a cost-minimisation approach (CMA) comparing erenumab to galcanezumab and fremanezumab on the basis that erenumab was non-inferior to galcanezumab and fremanezumab in terms of effectiveness and safety.

6.54 The resubmission did not present a CMA compared to eptinezumab.

6.55 The equi-effective doses were estimated as:

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- Erenumab 70 mg / 140 mg every 4 weeks.
- Galcanezumab 240 mg given at Day 0, followed by 120 mg every month.
- Fremanezumab 225 mg every month.

6.56 The resubmission claimed that the comparator dosing regimens reflected in these relativities were consistent with the regimens applied in previous CMAs considered by the PBAC (Table 2, Fremanezumab PSD, March 2020 PBAC Meeting; Table 10, Eptinezumab PSD, July 2022 PBAC meeting).

6.57 The resubmission did not consider any other additional costs or cost offsets.

6.58 Table 13 presents the results of the CMA. The CMA assumed dosing every 30 days for galcanezumab and fremanezumab, rather than monthly as specified in the equi-effective doses (see paragraph 6.55). This resulted in a higher number of doses for galcanezumab (25.35 rather than 25) and fremanezumab (24.35 rather than 24). The Pre-Sub-Committee Response (PSCR) stated that the exact definition of ‘monthly cycle’ had room for interpretation, and that 30-day reinjection cycles were previously accepted for galcanezumab (July 2019) and eptinezumab (July 2022). It was noted that the March 2020 and November 2022 fremanezumab submissions assumed 24 doses over 2 years.

Table 13: Results of the cost-minimisation approach (published effective prices)

Component	ERE	GAL	FREM
Cost per dose (AEMP)	\$453.09	\$463.00 ^a	\$488.89 ^a
Dose duration	2 years	2 years	2 years
Units (doses) over 2 years	26.09	25.35	24.35
Total medicine cost over 2 years (AEMP)	\$11,820.79 ^b	\$11,737.05	\$11,904.47
Average total medicine cost over 2 years (AEMP)	-	\$11,820.76	
Difference in total medicine cost vs erenumab over 2 years (AEMP)	-	-\$83.74	\$83.68

Source: Tables 3.2 and 3.4, pp112-113 of the resubmission.

AEMP = Approved ex-manufacturer price; ERE = erenumab; FREM = fremanezumab; GAL = galcanezumab.

^a AEMP as of June 2024.

^b \$453.09 x (365.25/28)*2

6.59 The resubmission estimated an average of the total medicine cost over 2 years of galcanezumab and fremanezumab to estimate the cost per dose of erenumab. This resulted in a higher price for erenumab than for galcanezumab. The submission did not present clinical evidence to justify a higher cost than galcanezumab.

Drug cost/patient/year

6.60 Table 14 presents the estimated drug cost per patient per year based on the published prices.

Table 14: Drug cost per patient for erenumab and galcanezumab and fremanezumab

	ERENUMAB			GALCANEZUMAB			FREMANEZUMAB		
	Trial	Model	Financials	Trial	Model	Financials	Trial	Model	Financials
Mean dose	70 mg or 140 mg per cycle			240 mg per cycle or 240 mg at Day 0 then 120 mg per cycle	240 mg at Day 0 then 120 mg per cycle		675 mg per 3-month cycle or 675 mg at Day 0 then 225 mg per 1-month cycle	225 mg per cycle	
Cycle length	28 days			30 days			30 days		
Cost/patient/cycle	\$520 ^a	\$453 ^b	\$520 ^a	\$523 ^c	\$463 ^d	\$523 ^c	\$560 ^c	\$489 ^d	\$560 ^c
Cost/patient/year	\$6,783 ^e	\$5,910 ^f	\$6,783 ^e	\$6,368 ^e	\$5,869 ^f	\$6,368 ^e	\$6,818 ^e	\$5,952 ^f	\$6,818 ^e

Source: Table 3.4, p113, Table 4.15, p125 of the resubmission, and calculated during the evaluation.

AEMP = Approved ex-manufacturer price; DPMQ=dispensed price for maximum quantity; EPTI = eptinezumab; ERE = erenumab; FREM = fremanezumab; GAL = galcanezumab; PBAC = Pharmaceutical Benefits Advisory Committee; pm = per month.

^a Cost-minimised DPMQ

^b Cost-minimised AEMP

^c Published DPMQ

^d Published AEMP

^e Cost/patient/cycle * 365.25/cycle length

^f Total medicine cost over 2 years (AEMP) / 2

Estimated PBS usage & financial implications

6.61 This resubmission was not considered by the DUSC.

6.62 The resubmission used a mixed epidemiology and market share approach to estimate the utilisation and financial impacts associated with the PBS listing of erenumab for the treatment of chronic migraine. This approach was taken because the fremanezumab PBS listing was expanded to include HFEM in November 2023, and so PBS script data following this change was inclusive of the chronic migraine and HFEM indications.

6.63 The resubmission performed the following steps to estimate the total number of scripts:

- Estimated the number of patients treated based on information presented in the PSD of the November 2020 PBAC submission for galcanezumab as treatment for chronic migraine.
- Estimated the number of scripts for chronic migraine if all patients were treated with galcanezumab.
- Predicted market growth if all patients were treated with galcanezumab.
- Conducted a market share analysis for galcanezumab, fremanezumab and eptinezumab under the status quo scenario.
- Predicted market share for galcanezumab, fremanezumab, eptinezumab and erenumab in the scenario where erenumab is listed on the PBS.

6.64 Table 15 presents the key inputs relied on in the financial estimates.

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Table 15: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Population aged above 18 years, prevalence of migraine, % with chronic migraine, % failed ≥ 3 prior treatments, uptake of botulinum toxin type A and galcanezumab.	Various	Various published sources and Galcanezumab, PSD, November 2020 PBAC meeting.	The data sources were appropriate.
Initial response and treatment persistence, proposed	Initial response at 3 months = not applied Persistence = 86% at the end of Year 1, declining to 61% at the end of Year 6	Table 4, Galcanezumab, PSD, November 2020 PBAC meeting.	This was uncertain.
Annual growth in galcanezumab scripts	14,727	Projection based on a linear trend	This was uncertain and based on the difference in projected scripts between 2025 and 2026. ^a
Treatment utilization			
Market share under the status quo scenario (i.e. without the listing of erenumab on the PBS)	Galcanezumab & fremanezumab: Yr 1-4: 45% Eptinezumab: Yr 1-4: 10%	Assumed based on PBS usage data (2021-2023).	This was uncertain given that eptinezumab was listed on the 1 August 2023 and PBS usage was confounded by galcanezumab experiencing medicine shortages.
Market share under the proposed scenario (i.e. with the listing of erenumab on the PBS)	Erenumab: Yr 1: 10% to Yr 6: 30% Galcanezumab & fremanezumab: Yr 1: 40% to Yr 6: 30% Eptinezumab: Yr 1 - 6: 10%	Assumed	This was uncertain.
Costs			
Erenumab (initiation and continuation)	\$519.98	Requested cost-minimised price (DPMQ)	-
MBS costs	\$0	-	-

Source: Table 4.3 p116, p120, Table 4.10 and 4.11 p122, and Table 4.15 p125 of the resubmission and sheet "8. ABS population" of file "Erenumab CM Section 4 July 2024 PBAC.xlsx"

DPMQ = dispensed price for maximum quantity; DUSC = Drug Utilisation Sub Committee; HFEM = high-frequency episodic migraine; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a Cell E75, Sheet "Novartis BIM" in "Erenumab CM Section 4 July 2024 PBAC.xlsx"

- 6.65 The resubmission estimated that the number of patients initiating galcanezumab was 5,000 to < 10,000 in 2021 and 5,000 to < 10,000 in 2022 and that the number of scripts was 80,000 to < 90,000 in 2021 and 100,000 to < 200,000 in 2022.
- 6.66 The resubmission predicted the growth in the number of scripts for chronic migraine if all patients were treated with galcanezumab by assuming a growth of 14,277 scripts per annum based on a linear trend.
- 6.67 The resubmission conducted a market share analysis to estimate the number of scripts dispensed of galcanezumab, fremanezumab, and eptinezumab under the status quo scenario (i.e., without the listing of erenumab on the PBS). Uncertainties with this approach included that eptinezumab was listed on the 1 August 2023 (eptinezumab

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represented 3% of all PBS scripts for CGRP medications from January to April 2024) and PBS usage was confounded by galcanezumab experiencing medicine shortages in late 2022.

6.68 The resubmission conducted a market share analysis to estimate the number of scripts dispensed of erenumab, galcanezumab, fremanezumab, and eptinezumab under the proposed scenario (i.e., with the listing of erenumab on the PBS). The resubmission stated the total market size for the CGRP inhibitors for the treatment of chronic migraine is not expected to grow because of the proposed erenumab listing.

6.69 Table 16 presents the estimated use and financial implications to the PBS/RPBS of listing erenumab.

Table 16: Estimated use and financial implications (cost-minimised prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed ^a	█ ¹	█ ²	█ ³	█ ⁴	█ ⁵	█ ⁶
Estimated financial implications of erenumab						
Cost to PBS/RPBS less copayments	\$█ ⁷	\$█ ⁸	\$█ ⁸	\$█ ⁹	\$█ ¹⁰	\$█ ¹¹
Estimated financial implications for galcanezumab, fremanezumab and eptinezumab						
Cost to PBS/RPBS less copayments	\$█ ⁷	\$█ ⁸	\$█ ⁸	\$█ ⁹	\$█ ¹⁰	\$█ ¹¹
Net financial implications						
Net cost to PBS/RPBS	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²
Net cost to MBS	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²
Net cost to PBS/RPBS/MBS	\$█¹²	\$█¹²	\$█¹²	\$█¹²	\$█¹²	\$█¹²

Source: Table 4.14, p124, Table 4.19, p127, Table 4.21, p128, Table 4.23, p129 of the resubmission and Table 17, erenumab, PBAC minutes, March 2019 PBAC meeting.

MBS = Medicare Benefits Schedule; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

¹ 20,000 to < 30,000

² 40,000 to < 50,000

³ 50,000 to < 60,000

⁴ 70,000 to < 80,000

⁵ 90,000 to < 100,000

⁶ 100,000 to < 200,000

⁷ \$10 million to < \$20 million

⁸ \$20 million to < \$30 million

⁹ \$30 million to < \$40 million

¹⁰ \$40 million to < \$50 million

¹¹ \$50 million to < \$60 million

¹² \$0 to < \$10 million

6.70 There was a net cost of listing erenumab on the PBS of \$0 to < \$10 million in Year 1, \$0 to < \$10 million in Year 6 and totalling \$0 to < \$10 million over the first 6 years of listing. The cost-minimised price of erenumab was based on the average of the cost-minimised AEMPs of erenumab versus galcanezumab and fremanezumab. As a result, the cost-minimised price of erenumab led to a higher cost over 2 years compared to galcanezumab and a lower cost over 2 years compared to fremanezumab. Each galcanezumab script substituted for erenumab incurred a cost to the PBS (see paragraph 6.72).

- 6.71 The resubmission proposed a grandfather clause. The resubmission claimed there are around < 500 patients currently receiving erenumab as a part of the access program in Australia. The resubmission also noted that there is a private demand for erenumab despite other CGRP medications being listed on the PBS, suggesting a clinical and patient need for access to an additional CGRP inhibitor. These patients would also be able to transition to PBS listed treatment.
- 6.72 The PSCR stated that increased substitution from fremanezumab to erenumab would result in cost savings to the PBS/RPBS. It was noted that the data was confounded by galcanezumab experiencing medicine shortages and by the recent expanding of the fremanezumab PBS listing to include HFEM.

Financial Management – Risk Sharing Arrangements

- 6.73 The resubmission noted that there is a risk-sharing arrangement (RSA) with expenditure caps for all CGRP medications. The resubmission proposed erenumab enter the existing RSA. This would minimise uncertainty regarding the duration of treatment and uptake, and the cost of usage outside the PBS criteria to the treatment of patients with episodic migraine and market growth due to the sequential use of CGRP medications.

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

7 PBAC Outcome

- 7.1 The PBAC recommended erenumab for the prophylactic treatment of chronic migraine in adults who have experienced an inadequate response, intolerance or a contraindication to at least 3 prophylactic migraine medications. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of erenumab would be acceptable if it were cost minimised to the least costly alternative therapy of the nominated comparators, galcanezumab, fremanezumab and eptinezumab. The PBAC considered that erenumab was non-inferior in terms of efficacy and safety compared to the nominated comparators. The PBAC advised that erenumab should join the existing risk sharing arrangement (RSA) for this class of medicines with no increase to the expenditure caps. The PBAC considered erenumab could be listed for treatment-resistant migraine.
- 7.2 The PBAC noted the substantial number of comments from individuals, a health professional and an organisation that supported the resubmission and highlighted the need for additional, effective treatment options for migraine.
- 7.3 The PBAC considered that the nominated comparators of galcanezumab, fremanezumab and eptinezumab were appropriate.
- 7.4 The PBAC noted the resubmission provided clinical evidence for erenumab versus placebo for the treatment of chronic migraine from one primary randomised controlled trial (Study 295) and two supplementary randomised controlled trials (DRAGON and Study 609). The PBAC noted that both erenumab 70 mg and 140 mg

were associated with a statistically significant reduction in the number of monthly migraine days (MMDs) from baseline to 12 weeks (MD = -2.46; 95% CI: -3.52, -1.39 and MD = -2.45; 95% CI: -3.51, -1.38 respectively) in Study 295. The mean difference exceeded the minimal clinically important difference (MCID) of 2 days. The PBAC also noted that a meta-analysis of the three erenumab trials found a statistically significant greater reduction in the change in MMDs for erenumab 70 mg compared to placebo (MD = -2.20; 95% CI: -2.84, -1.55) and that the mean difference exceeded the MCID of 2 days. The PBAC noted that the *post-hoc* subgroup analysis of patients treated with erenumab 70 mg who had experienced ≥ 3 treatment failures reported similar results (MD = -2.59; 95% CI: -4.48, -0.70). The PBAC considered that erenumab resulted in a clinically significant reduction in the number of the MMDs compared to placebo in patients with chronic migraine.

- 7.5 The PBAC noted that the resubmission was primarily based on indirect treatment comparisons (ITCs) comparing erenumab (1 trial) with galcanezumab (2 trials), fremanezumab (3 trials) and eptinezumab (3 trials). Placebo was the common comparator. The PBAC noted that the subgroup analyses of patients with chronic migraine were pre-specified and that *post hoc* subgroup analyses were presented for patients who had failed ≥ 3 prophylactic migraine medications. The PBAC noted that this approach aligned with the listing of the comparator treatments and considered that it was appropriate.
- 7.6 The PBAC noted that the majority of the ITCs resulted in no statistically significant differences in the reduction in the MMDs (see Table 7 and Table 9) or the number of patients experiencing a $\geq 50\%$ reduction in mean monthly migraine days (see Table 8 and Table 10) in both the chronic migraine populations and the ≥ 3 treatment failure *post hoc* subgroup populations. The PBAC also noted that for most of the comparisons, the upper 95% confidence intervals were less than the nominated non-inferiority margin of 2 days, which further supported the claim of non-inferiority. The PBAC noted that the upper 95% confidence interval exceeded the non-inferiority margin of 2 days for comparisons between erenumab and galcanezumab for both the chronic migraine and the ≥ 3 treatment failure subgroup populations.
- 7.7 The PBAC also noted that there were multiple differences between the 9 trials relating to the population/eligibility criteria, patient demographics, setting, duration of treatment and outcomes measures (see paragraph 6.17) that reduced the transitivity. In addition, the PBAC noted that there was considerable variation in the placebo responses across the trials.
- 7.8 On balance, the PBAC considered that the claim that erenumab was non-inferior in terms of effectiveness compared to galcanezumab, fremanezumab and eptinezumab, was reasonably supported by the clinical evidence presented.
- 7.9 The PBAC considered that the claim that erenumab was non-inferior compared to galcanezumab, fremanezumab and eptinezumab in terms of comparative safety was reasonably supported by the clinical evidence presented.

- 7.10 The PBAC noted that the resubmission presented a cost minimisation approach (CMA) versus galcanezumab and fremanezumab, based on 50% use of fremanezumab and galcanezumab which resulted in a higher price for erenumab than for galcanezumab. The PBAC noted no evidence was provided to support erenumab having a higher price than any alternative therapy. The PBAC considered that erenumab would be cost-effective if it were cost-minimised to the lowest cost alternative therapy (using effective prices).
- 7.11 The PBAC considered that the equi-effective doses of erenumab and the alternative therapies were:
- Erenumab 70 mg or 140 mg every 4 weeks
 - Galcanezumab 240 mg on Day 0, followed by 120 mg every month
 - Fremanezumab 225 mg every month
 - Eptinezumab 100 mg every 12 weeks
- 7.12 The PBAC considered that the methodology for the CMA presented in the resubmission was reasonable, noting that the number of doses should reflect the equi-effective dosing.
- 7.13 The PBAC considered that, given its recommendation was on a cost-minimisation basis to the least costly alternative therapy, the utilisation estimates for the use of erenumab for chronic migraine were reasonable and that the listing was likely to be cost neutral.
- 7.14 The PBAC considered that it was appropriate for erenumab to be added to the RSA in place for galcanezumab, fremanezumab and eptinezumab with no increase to the expenditure caps.
- 7.15 The PBAC advised that treatment with erenumab should be initiated by a neurologist or by a general practitioner in consultation with a neurologist, as per the restriction change which was implemented on 1 November 2024 for galcanezumab, fremanezumab and eptinezumab. The PBAC considered that patients currently accessing erenumab via the patient access program or privately should be able to meet the initial restriction criteria and that a grandfather restriction was not required.
- 7.16 The PBAC noted that fremanezumab is currently listed for the indication of treatment-resistant migraine, which includes high-frequency episodic migraine in addition to chronic migraine. The PBAC noted that galcanezumab was recommended for this indication in March 2022 (see paragraph 2.3). Noting that the (i) claim of non-inferior efficacy and safety was unlikely to be different in the high-frequency episodic migraine population, and (ii) the unit cost of fremanezumab for high-frequency episodic migraine is the same as for chronic migraine, therefore the cost-effectiveness in this population is unlikely to be different, the PBAC recommended that erenumab could also be listed with the indication of treatment-resistant migraine and a restriction that aligned with that for fremanezumab.

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- 7.17 The PBAC recommended that erenumab should be treated as interchangeable on an individual patient basis with galcanezumab, fremanezumab and eptinezumab.
- 7.18 The PBAC advised that erenumab is not suitable for prescribing by nurse practitioners.
- 7.19 The PBAC recommended that the Early Supply Rule should apply.
- 7.20 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because erenumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over galcanezumab, fremanezumab or eptinezumab, or not expected to address a high and urgent unmet clinical need given the presence of alternative therapies, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.21 The PBAC advised that erenumab is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item

Either for (a) chronic migraine indication:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
ERENUMAB					
erenumab 70 mg/mL injection, 1 mL pen device	NEW MP	1	1	2	Aimovig
erenumab 140 mg/mL injection, 1 mL pen device	NEW MP	1	1	2	Aimovig
	Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Benefit type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [existing code:16018]				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
Restriction Summary / Treatment of Concept:					
	Indication: Chronic migraine				
	Treatment Phase: Initial treatment				
	Treatment criteria:				
	Must be treated by a neurologist; OR				

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	Must be treated by a general practitioner in consultation with a neurologist
	AND
	Treatment criteria:
	Patient must not be undergoing concurrent treatment with the following PBS benefits: (i) botulinum toxin type A listed for this PBS indication, (ii) another drug in the same pharmacological class as this drug listed for this PBS indication
	Clinical criteria:
	Patient must have experienced an average of 15 or more headache days per month, with at least 8 days of migraine, over a period of at least 6 months, prior to commencement of treatment with this medicine for this condition
	AND
	Clinical criteria:
	Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must be appropriately managed by their practitioner for medication overuse headache, prior to initiation of treatment with this drug
	AND
	Population criteria:
	Patient must be at least 18 years of age.
	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

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
ERENUMAB					
erenumab 70 mg/mL injection, 1 mL pen device	NEW MP	1	1	5	Aimovig
erenumab 140 mg/mL injection, 1 mL pen device	NEW MP	1	1	5	Aimovig
	Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Benefit type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [existing code:12029]				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
Restriction Summary / Treatment of Concept:					
	Indication: Chronic migraine				
	Treatment Phase: Continuing treatment				
	Treatment criteria:				

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	Must be treated by a specialist neurologist or in consultation with a specialist neurologist
	AND
	Treatment criteria:
	Patient must not be undergoing concurrent treatment with the following PBS benefits: (i) botulinum toxin type A listed for this PBS indication, (ii) another drug in the same pharmacological class as this drug listed for this PBS indication
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine days per month
	AND
	Clinical criteria:
	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

Or for (b) treatment-resistant migraine indication:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ERENUMAB					
erenumab 70 mg/mL injection, 1 mL pen device	NEW MP	1	1	2	Aimovig
erenumab 140 mg/mL injection, 1 mL pen device	NEW MP	1	1	2	Aimovig
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [Existing code: 16104]					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Restriction Summary / Treatment of Concept:					
Indication: Treatment-resistant migraine					
Treatment Phase: Initial treatment					
Treatment criteria:					
Must be treated by a neurologist; or					
Must be treated by a general practitioner in consultation with a neurologist					
AND					
Treatment criteria:					
Patient must not be undergoing concurrent treatment with the following PBS benefits: (i) botulinum toxin type A listed for this PBS indication, (ii) another drug in the same pharmacological class as this drug listed for this PBS indication					
Clinical criteria:					

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Patient must have experienced at least 8 migraine headache days per month, over a period of at least 6 months, prior to commencement of treatment with this medicine for this condition
AND
Clinical criteria:
Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with this drug for this condition
AND
Clinical criteria:
Patient must be appropriately managed by their practitioner for medication overuse headache, prior to initiation of treatment with this drug
Population criteria:
Patient must be at least 18 years of age
Prescribing instructions: Prophylactic migraine medications are propranolol, amitriptyline, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate or topiramate.
Prescribing instructions: Patient must have the number of migraine headache days per month documented in their medical records.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ERENUMAB					
erenumab 70 mg/mL injection, 1 mL pen device	NEW MP	1	1	5	Aimovig
erenumab 140 mg/mL injection, 1 mL pen device	NEW MP	1	1	5	Aimovig
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (Streamlined) [Existing code: 14563]					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Restriction Summary / Treatment of Concept:					
Indication: Treatment-resistant migraine					
Treatment Phase: Continuing treatment					
Treatment criteria:					
Must be treated by a neurologist; or					
Must be treated by a general practitioner in consultation with a neurologist					
AND					
Treatment criteria:					
Patient must not be undergoing concurrent treatment with the following PBS benefits: (i) botulinum toxin type A listed for this PBS indication, (ii) another drug in the same pharmacological class as this drug listed for this PBS indication					
Clinical criteria:					
Patient must have previously received PBS-subsidised treatment with this drug for this condition					

	AND
	Clinical criteria:
	Patient must have achieved and maintained at least 50% reduction from baseline in the number of migraine headache days per month
	AND
	Clinical criteria:
	Patient must continue to be appropriately managed for medication overuse headache
	Prescribing instructions:
	Patient must have the number of migraine headache days per month documented in their medical records.

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

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.