7.05 ERENUMAB

Injection 70 mg in 1 mL single dose pre-filled pen, Aimovig®, Novartis Pharmaceuticals

1 Purpose of Application

1.1 The resubmission requested an Authority Required (Streamlined) listing for erenumab for treatment of chronic migraine in patients who have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications. The first erenumab submission for chronic migraine was rejected in July 2018.

1.2 The resubmission requested listing on the basis of a cost-minimisation analysis versus botulinum toxin type A (Botox) and a cost-utility analysis versus best supportive care (BSC). The key components of the clinical issue addressed by the resubmission are presented in Table 1.

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

Component	Description
Population	Patients with chronic migraine.
Intervention	Erenumab; 140 mg administered once every 4 weeks as a subcutaneous injection.
Comparators	Botox; administered by injection every 12 weeks to 31-39 sites in the head. BSC.
Outcomes	Change from baseline in the number of monthly migraine days; proportion of responders (≥50% change from baseline); safety.
Clinical claim	Erenumab is non-inferior in terms of comparative effectiveness and comparative safety compared to Botox. Erenumab is superior in terms of comparative effectiveness and equivalent in terms of comparative safety compared to BSC.

BSC=best supportive care
Source: Table 1.1, p6 and Section 2.8.2, p88-89 of the resubmission.

2 Requested listing

2.1 The restriction criteria proposed in the submission is provided below with suggested deletions (strikethrough text) and additions (italic text) by the Secretariat.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
ERENUMAB 70 mg in 1.0mL solution for injection, 70 mg/1mL × 2 pre-filled pen	1	2	2, 5[a]	$[redacted][b]	Aimovig®, Novartis Pharmaceuticals

[a] Two repeats for initial therapy and 5 repeats for continuing therapy.
[b] $[redacted] is a weighted price based on the cost-minimisation price ($[redacted]) and the cost-effectiveness price ($[redacted]) weighted according to the relevant patient population (cost-minimisation: Botox ([redacted]%); cost-effectiveness: non-Botox ([redacted]%))

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Severity:	-
Condition	Migraine
PBS Indication:	*Chronic m~~M~~igraine*
Treatment phase:	Initial
Restriction: Section 85 *Authority required*	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	~~Must be prescribed by a neurologist or a pain/headache specialist.~~ *Must be treated by a specialist neurologist or specialist pain medicine physician accredited or experienced in treating headache.*
Clinical criteria:	Patient must have experienced at least 8 days of migraine per month, over a period of at least 6 months, prior to commencement of treatment with *this medicine* ~~erenumab;~~ AND Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with *this medicine* ~~erenumab~~; AND Patient must be appropriately managed ~~by his or her practitioner~~ for medication overuse headache, prior to initiation of treatment with *this medicine* ~~erenumab~~.
Population criteria:	~~Patient must be aged 18 years or older~~.
Prescriber instructions:	Prophylactic migraine medications are propanolol, amitriptyline, methysergide, pizotifen, cyproheptadine or topiramate. *Baseline measurement of the number of migraine days per month must be documented in the patient's medical records*
Administrative Advice	This drug is not PBS-subsidised for use in combination with botulinum toxin type A

Name, Restriction, Manner of administration and form	**Max. Qty packs**	**№.of Rpts**	**Proprietary Name and Manufacturer**	
erenumab, 70 mg/mL, 2×1mL, injection devices	1	5	Aimovig®	Novartis Pharmaceuticals

Erenumab (Aimovig®)	
Category / Program	GENERAL – General Schedule (Code GE)

Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	Chronic
Severity:	-
Condition	Migraine
PBS Indication:	*Chronic m~~M~~igraine*
Treatment phase:	Continuing
Restriction: Section 85 *Authority required*	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	Must be treated by or in consultation with a specialist neurologist or a specialist pain medicine physician accredited or experienced in treating headache.
Clinical criteria:	*Patient must have previously received PBS-subsidised initial 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 ~~after three treatment cycles (12 weeks duration)~~ in order to be eligible for continuing PBS-subsidised treatment; ~~OR~~ ~~*Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine days per month after six treatment cycles (24 weeks duration) in order to be eligible for subsequent continuing PBS-subsidised treatment;*~~ ~~OR~~ ~~Patient must have 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;~~ AND Patient must *continue to* be appropriately managed ~~by his or her practitioner~~ for medication overuse headache, ~~prior to initiation of treatment with erenumab.~~
Population criteria:	~~Patient must be aged 18 years or older~~.
Administrative Advice	This drug is not PBS-subsidised for use in combination with botulinum toxin type A.

2.2 The PBAC noted a number of changes to the requested restriction compared to the July 2018 requested restriction:

- Removal of the requirement that patients are naïve to Botox.

- Removal of the requirement that patients must experience an average of 15 or more headache days per month. The only frequency-based criterion remaining was that patients must have ≥8 migraine days per month over a period of at least 6 months. The PBAC considered the revised wording was inconsistent with the definition of chronic migraine (see paragraph 4.1).
- Shortening the initial response assessment timepoint to 12 weeks from the original 24 weeks.
- Altering of the response criterion to be ≥50% reduction in monthly migraine days, while the previous requested restriction used ≥50% reduction in monthly headache days.
- Continuing therapy to be prescribed by a neurologist or a pain/headache specialist, or a general practitioner (GP) in consultation with a neurologist or pain/headache specialist. The ESC considered that there would be clinical uncertainty in differentiating migraine days from headache days in practice and this would be particularly challenging for a GP continuing therapy, even in consultation with a specialist. The PBAC considered it may be appropriate to require the first continuing script to be prescribed by a neurologist or a pain/ headache specialist.

2.3 The DUSC noted the eligibility criteria for continuing treatment did not stipulate the use of any particular tool to assess response (e.g. a patient diary) and it is uncertain how prescribers will consistently assess patient response. The PBAC agreed with the DUSC and considered it may be appropriate for the restriction criteria to require patients to keep a headache diary to assess response to treatment.

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

2.5 The PBAC noted ~15% of patients in the BSC treatment arm of the pivotal study would meet the proposed continuation criteria, and treatment with erenumab only allowed an additional ~25% of patients to meet the criteria. In addition, there is no clear evidence for biological variation in treatment response in the first place and therefore it may be appropriate to remove the continuation rule and adjust (lower) the treatment-effect for the overall group.

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

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

3 Background

Registration status

3.1 Erenumab was approved for registration by the Therapeutic Goods Administration (TGA) on 2 July 2018 with the indication "…prophylaxis of migraine in adults".

3.2 The product information (PI) states that "The recommended dose of AIMOVIG is 70 mg injected subcutaneously once every 4 weeks. Some patients may benefit from a dosage of 140 mg injected subcutaneously once every 4 weeks." The submission only requested listing for the 140 mg dose of erenumab. The PBAC considered this was inappropriate and inconsistent with the recommended dosing of erenumab.

3.3 The resubmission presented results from the open-label extension (Study 255) of the pivotal trial for chronic migraine (Study 295), as well as pharmacokinetic and safety data to support the claim that the 140 mg dose demonstrates consistently higher reductions in migraine than the 70 mg dose with no additional safety or tolerability risks. Although very limited data was presented in the resubmission, the ESC and the PBAC considered that the differences in efficacy are not likely to be clinically significant for most patients and noted the higher prevalence of adverse effects with 140 mg than with 70 mg. The PBAC noted some outcomes were numerically better for the 140 mg dose than the 70 mg dose in the subgroup of patients with an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications but considered the use of the subgroup too uncertain and the patient numbers too small to draw conclusions.

3.4 As with the July 2018 submission, the clinical, economic and financial sections of the resubmission were based on the 140 mg dose only, given as 2 x 70 mg injections.

3.5 The resubmission indicated an application had been lodged with the TGA to register a 140 mg injection for erenumab and the pre-subcommittee response (PSCR) advised registration was expected October 2019. The PBAC noted in the pre-PBAC response that the Sponsor agreed to make both doses (70 mg and 140 mg) available for use through the PBS.

Previous PBAC consideration

3.6 Following is a summary of the key concerns identified in the July 2018 PBAC submission and the approach in the resubmission.

Table 2: Summary of outstanding matters of concern

Component	July 2018 submission	November 2018 resubmission
Requested PBS listing	No justification for excluding patients who had previously been treated with Botox. (paragraph 7.4 July 2018 PSD)	Patients who have been treated with Botox included. The ESC considered this was appropriate.
Clinical place/comparator	Re-evaluate and justify the clinical place of erenumab (paragraph 7.20 July 2018 PSD)	Resubmission has maintained erenumab as a last-line treatment option but has broadened the treatment population to include patients for whom Botox is not a treatment option. Botox remained as comparator and BSC added as a comparator for the non-Botox population.
Clinical evidence	PBAC considered the subgroup insufficient. (paragraph 7.11 July 2018 PSD)	Subgroup expanded to include patients who may have used Botox (N=163; 34.8% of Study 295).
Clinical claim	Superior comparative effectiveness and comparative safety over Botox was not accepted. (paragraph 7.11 July 2018 PSD)	Claim altered to non-inferior comparative effectiveness and safety over Botox and superior comparative effectiveness and equivalent comparative safety over BSC.
Economic evaluation	Use of a cost-utility analysis to assess the cost-effectiveness of erenumab over Botox was unreliable. Erenumab would be cost-effective with an ICER between $15,000-$45,000 per QALY (paragraphs 7.13 and 7.20 July 2018 PSD)	Cost-minimisation analysis versus Botox. Modelled analysis versus BSC. Estimated base case ICER: $[redacted]
Financial implications	Utilisation of erenumab and resulting financial impact were likely to have been significantly underestimated. (paragraph 7.19 July 2018 PSD)	Patient population has been broadened with estimated patient numbers increased to [redacted]. Estimated net cost to Government $[redacted] dollars over the initial 6 years following listing.

BSC=best supportive care; PSD=public summary document

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

4 Population and disease

4.1 Migraine is characterised by recurrent headache, lasting 4 to 72 hours and often accompanied by symptoms such as nausea, vomiting and hypersensitivity to light and sound. The target population for treatment with erenumab are adult patients with chronic migraine, defined as 15 or more headache days per month, at least 8 of which have to be typical migraine days. The TGA indication is not limited to chronic migraine.

4.2 The resubmission proposed erenumab as a treatment for patients who have failed to achieve an adequate response to at least three oral migraine prophylactic medications, or is intolerant to, or contraindicated for, the available migraine prophylactic medications. With this clinical positioning erenumab is expected to substitute for Botox or be used when Botox is not a treatment option, due to lack of access to neurologists or patient preference relating to the Botox injection schedule as previously noted by the PBAC (paragraph 7.8 July 2018 PSD).

4.3 The DUSC considered that while the total number of patients with chronic migraine is difficult to estimate the prevalence of chronic migraine is likely to be approximately 400,000 patients.

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

5 Comparator

5.1 Concordant with the clinical place for erenumab identified above by the resubmission, Botox has been maintained as a comparator and BSC has been added as the comparator for the patient population where Botox is not a treatment option.

5.2 The PBAC considered that Botox and BSC are reasonable comparators. However, the PBAC did not consider the weighting across the comparators ([redacted]% Botox, [redacted]% BSC) to be adequately supported. Further, the PBAC did not consider a differential price for the two groups of patients (those treated with Botox versus those not treated with Botox) to be adequately justified. The PBAC also noted that a proportion of patients may be treated with sequential use of erenumab and Botox.

For more detail on the 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 (258), health care professionals (4) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the debilitating physical, mental and social impact of chronic migraine. Comments from patients with experience with the use of erenumab describe a range of benefits of treatment including the ability to return to work, fewer side effects than currently available medications, decreased use of other medications, increased mood and an improved social life. Many patients expressed their concern at being able to afford the medicine if it was not listed on the PBS. The health care professionals described observing a range of benefits from erenumab treatment in their chronic migraine patients with several respondents also acknowledging it does not work in everyone.

6.3 The PBAC noted the advice received from Headache Australia clarifying the likely use of erenumab in clinical practice. The PBAC specifically noted the advice that erenumab should only be prescribed by neurologists and pain specialists and the statement that it would be preferred that both the 70 mg and 140 mg doses are made available.

6.4 The PBAC noted the support received from the Australian and New Zealand Headache Society (ANZHS) for listing erenumab on the PBS.

Clinical trials

6.5 As for the July 2018 submission, the resubmission was based on one erenumab trial, Study 295 (N=476), and two Botox trials, PREEMPT I (N=679) and PREEMPT II (N=705).

The resubmission also included evidence from Study 255, the open label extension of Study 295.

6.6 The direct comparison versus BSC and the indirect comparison versus Botox were based on a post-hoc subgroup selected to correspond to the requested PBS restriction, i.e. patients who had failed, were intolerant or contraindicated to ≥3 prophylactic medications.

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

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Erenumab		
Study 295	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 JL et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial.	Amgen, Inc Clinical Study Report September 2016 clinicaltrials.gov identifier: NCT02066415 Lancet Neurol 2017; 16: 425-34.
Study 255	An Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 334.	Amgen, Inc Clinical Study Report November 2017 clinicaltrials.gov identifier: NCT02174861
Botox		
PREEMPT I	Aurora SK, Dodick DW, Turkel CC, DeGryse Re et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial.	Cephalalgia 2010; 30(7): 793-803.
PREEMPT II	Diener et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial.	Cephalalgia 2010; 30(7): 804-814.
PREEMPT 1 and PREEMPT II pooled analysis	Dodick DW, Turkel CC, DeGryse RE, Aurora SK et al. OnabotulinumtoxinA treatment reduce headache duration in adults with chronic migraine: Pooled results from the double-blind, randomized, placebo-controlled phase of the PREEMPT clinical program.	Headache 2010; 50: 58-59.

Source: Table 2.9, p29-34 of the resubmission.

6.8 The key features of the randomised trials included in the direct comparison versus BSC and the indirect comparison versus Botox are provided in the table below. As the subgroup analysis presented by the submission formed the basis of the clinical claim, information relating to the subgroup is included in the table.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Erenumab vs. placebo						
Study 295	476 (subgrp=163)	R, DB, MC 12 weeks	Low	Failed ≥3 prophylactic medications	Change from baseline in monthly migraine days	≥50% responder for change in headache days; AEs
Botox vs. placebo						
PREEMPT I and PREEMPT II pooled analysis	1,384 (subgrp=396 or 479[a])	R, DB, MC 24 weeks	Low	Failed ≥3 prophylactic medications	Change from baseline in headache days	Not used

[a] The size of the subgroup varied depending on the outcome assessed. The analysis of change in headache days used N=396 and analysis of ≥50% responder rate used N=479.

AEs=adverse events; DB=double blind; MC=multi-centre; R=randomised; subgrp=subgroup

Source: Compiled from Section 2 of the resubmission.

6.9 Removal of the requirement that erenumab patients be naïve to Botox increased the number of patients in the subgroup from [redacted] ([redacted]% of the ITT population) in the July 2018 submission to 163 (34%) in the resubmission.

6.10 While the subgroup had increased in size, there remained a number of concerns with the use of subgroup data for both the direct and the indirect comparisons:

- Patients with no therapeutic response to ≥3 prophylactic medicines were excluded from Study 295 and it was therefore unclear how representative this subgroup will be of the population that will be treated with erenumab in clinical practice. Patients with ≥3 treatment failures could have been included in the trial. The difference between 'no therapeutic response' and 'treatment failure' was likely to have been a subjective assessment by each individual investigator.
- While a number of subgroup analyses were planned in Study 295 (i.e., patients with none, ≥1 or ≥2 failed prior therapies), the subgroup analysis of patients with ≥3 failed prophylactic medicines was a post-hoc analysis.
- Effectiveness outcomes were sourced from the subgroup population but safety outcomes in the submission were based on the overall trial population. The resubmission did not provide any information on treatment exposure or safety for the nominated subgroup. As the subgroup is a patient population that has failed previous medications, it may not be reasonable to assume a similar exposure to treatment or safety profile in this population. The PSCR provided some safety data for the subgroup (see paragraph 6.20).
- The subgroup was selected to reflect the proposed PBS listing criteria but removal of the requirement to have more than 15 headache days per month in the criteria did not reflect the inclusion criteria of the trial which required patients to have more than 15 headache days per month of which 8 or more were migraine days.

6.11 The PBAC considered the use of a small subgroup of patients in the pivotal trial instead of the ITT population for the clinical claim in the resubmission was poorly justified and considered there were significant applicability issues with the subgroup that was used.

6.12 The PBAC noted that patients were excluded from the clinical study if they were using a number of commonly used prophylactic medications for migraine which may also limit the applicability of the clinical data to the population of patients that will be treated with erenumab.

Comparative effectiveness – erenumab vs. BSC

6.13 Results of the comparison of erenumab and BSC, based on the nominated post-hoc subgroup of patients who had failed ≥3 prophylactic medications, are provided in the table below. The resubmission provided results for change from baseline in monthly migraine days, headache days and acute medication treatment days, as well as proportion of patients with ≥50% reduction in migraine and headache days.

Table 5: Subgroup results for the erenumab – BSC comparison in Study 295

Outcome	Erenumab 140 mg (N=65)		Placebo (N=96)		Mean difference (95% CI)
	Baseline (mean±SD)	Change (mean±SE)	Baseline (mean±SD)	Change (mean±SE)	
Change from baseline					
Monthly migraine days	19.0±4.7	-7.0±0.9	18.4±4.5	-2.8±0.6	**-4.2 (-6.3,-2.1)**
Monthly headache days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute medication days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Erenumab 140 mg n with event/N (%)		**Placebo n with event/N (%)**		**OR (95% CI)**
≥50% responder					
Migraine days	25/65 (38.5%)		15/98 (15.3%)		**3.48 (1.64, 7.39)**
Headache days	[redacted]		[redacted]		[redacted]

CI=confidence interval; OR=odds ratio; SD=standard deviation; SE=standard error; **bold**=statistically significant
Source: Table 2.34 and Table 2.35, p73 of the resubmission.

6.14 The analyses showed statistically significant advantages for erenumab compared to placebo across all outcomes presented.

6.15 In the subgroup of patients, the ESC noted a mean reduction in MMD of 5.4 days for the 70 mg dose [mean difference vs placebo - 2.6 days (95%CI: -4.5, -0.7)] with 34.8% of patients achieving a ≥50% reduction in MMD [OR vs placebo 2.96 (95%CI: 1.39, 6.27)][2]. The mean reduction in MMD for the 140 mg dose was 7.0 days [mean difference vs placebo -4.2 (95%CI: -6.3, -2.1)] with 38.5% of patients achieving a ≥50% reduction in MMD [OR vs placebo 3.48 (95%CI: 1.64, 7.39)].

6.16 The ITT results for Study 295 for the 70 mg and 140 mg dose are presented in Table 6. The PBAC noted the mean change from baseline in monthly migraine days (the primary endpoint) were similar for the 70 mg and 140 mg dose.

Table 6: Efficacy outcomes for erenumab 70 mg and 140 mg, ITT population, Study 295

Outcome at 12 weeks	Placebo n=281	Erenumab 70 mg n=188		Erenumab 140 mg n=187	
	Change from baseline	Change from baseline	Mean difference vs placebo	Change from baseline	Mean difference vs placebo
Monthly migraine days	-4.18 (-4.86,-3.50)	-6.64 (-7.47, -5.81)	-2.46 (-3.52, -1.39)	-6.63 (-7.45, -5.80)	-2.45 (-3.51, -1.38)
Monthly headache days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	50% responder	**50% responder**	**OR vs placebo**	**50% responder**	**OR vs placebo**
Monthly migraine days	23.5%	39.9%	2.18 (1.46,3.27)	41.2%	2.34 (1.56, 3.51)
Monthly headache days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NA=not available; OR=odds ratio
Source: compiled during evaluation. Table 10-1, pg 54, CSR; table 10-5, pg 61, CSR; Table 14-4.4.7, pg 281. Monthly headache days 50% responder data from submission (Table 2.24, pg 61) (results for 70 mg dose not presented in the submission).

[2] Attachment 15 of the resubmission, pg 1-2

Comparative effectiveness – erenumab vs. Botox

6.17 The results of the indirect comparison of erenumab and Botox based on the subgroup, comparing change from baseline in monthly headache days and proportion of patients with ≥50% reduction in mean headache days, are provided in the table below.

Table 7: **Indirect comparisons - change from baseline in monthly headache days and ≥50% reduction in monthly headache days: subgroup**

Trial	Mean change from baseline (SD) in monthly headache days			Treatment effect WMD (95% CI)
	Erenumab 140 mg	Placebo	Botox	
Study 295 (12 weeks)	N=65 [redacted] ([redacted])	N=96 [redacted] ([redacted])	[redacted]	[redacted] ([redacted], [redacted])
Pooled PREEMPT trials (24 weeks)	-	N=248 -4.7 (6.4)	N=231 -7.4 (6.6)	**-2.70 (-3.87, -1.53)**
Indirect mean difference (random effects)				[redacted] ([redacted], [redacted])
	≥50% reduction in monthly headache days n with event/N (%)			**Treatment effect**
	Erenumab 140 mg	**Placebo**	**Botox**	**OR (95% CI)** / **RR (95% CI)**
Study 295 (12 weeks)	[redacted]/65 ([redacted]%)	[redacted]/98 ([redacted]%)	[redacted]	[redacted] ([redacted], [redacted]) / [redacted] ([redacted], [redacted])
Pooled PREEMPT trials (24 weeks)	-	51/207 (24.6%)	76/189 (40.2%)	**2.06 (1.34, 3.16)** / **1.63 (1.22, 2.19)**
Indirect comparison (random effects)				[redacted] ([redacted], [redacted]) / [redacted] ([redacted], [redacted])

Source: Table 2.37, p76; Table 2.38, p77 of the resubmission.
CI=confidence interval; OR=odds ratio; RR=relative risk; SD=standard deviation; WMD=weighted mean difference; **bold**=statistically significant

6.18 While the indirect comparison demonstrated no statistically significant differences between the two agents, there are a number of concerns with the comparison:

- The response in the placebo arm in the pooled Botox trials was considerably higher than the placebo response in Study 295 for both outcomes. As such, the comparison did not meet the assumption of transitivity.
- Change from baseline in monthly headache days was an exploratory outcome in Study 295 while proportion of patients with ≥50% reduction in monthly headache days was not defined as a primary, secondary or exploratory outcome in Study 295 and the resubmission has provided no information on how the outcome was calculated.
- The timepoint for analysis was 12 weeks in Study 295 for erenumab and 24 weeks for the Botox trials. The resubmission argued that the comparison is conservative, as the open label extension trial Study 255 has shown an improvement in response over time with erenumab. The PBAC noted evidence from Study 255 was not powered to demonstrate an improvement in erenumab response over time (incidence of AEs was its primary outcome).

6.19 The resubmission also provided results for the indirect comparison using the overall trial populations (Table 8). As for the subgroup population, the indirect comparison of erenumab and Botox showed no statistically significant difference for change in monthly headache days or proportion of patients with ≥50% reduction in headache days. As for the subgroup comparison (Table 7), the response in the placebo arm of

the PREEMPT trials was considerably higher than that observed in the placebo arm of the erenumab trial which may impact on the validity of the indirect comparison.

Table 8: Indirect comparisons - change from baseline in monthly headache days and ≥50% reduction in monthly headache days: overall trial population

Trial	Mean change from baseline (SD) in monthly headache days			Treatment effect WMD (95% CI)	
	Erenumab 140 mg	Placebo	Botox		
Study 295 (12 weeks)	N=187 -7.02 (5.74)	N=281 [redacted] ([redacted])	-	[redacted] ([redacted], [redacted])	
Pooled PREEMPT trials (24 weeks)	-	N=688 -6.6 (6.7)	N=696 -8.4 (6.6)	**-1.86 (-2.74, -0.98)**	
Indirect mean difference (random effects)				[redacted] ([redacted], [redacted])	
	≥50% reduction in monthly headache days n with event/N (%)			**Treatment effect**	
	Erenumab 140 mg	**Placebo**	**Botox**	**OR (95% CI)**	**RR (95% CI)**
Study 295 (12 weeks)	[redacted]/187 (33.2%)	[redacted]/281 (20.3%)	-	[redacted] ([redacted], [redacted])	[redacted] ([redacted], [redacted])
Pooled PREEMPT trials (24 weeks)	-	244/696 (35.1%)	323/688 (47.0%)	**1.64 (1.32, 2.03)**	**1.34 (1.18, 1.52)**
Indirect comparison (random effects)				[redacted] ([redacted], [redacted])	[redacted] ([redacted], [redacted])

Source: Table 2.39, p78; Table 2.40, p79 of the resubmission.
CI=confidence interval; OR=odds ratio; RR=relative risk; SD=standard deviation; WMD=weighted mean difference

Comparative harms – erenumab vs. BSC

6.20 The resubmission did not provide any comparisons based on the subgroup population for safety outcomes. The PSCR presented a comparison of the safety of erenumab 140 mg and placebo in the ITT population and the subgroup. The PBAC noted, although based on a small sample size, there was a greater occurrence of any AE for the subgroup population (60.0%, n=65) than had been observed in the overall trial population (46.8%, n=188).

Table 9: Comparison of AEs (total trial population vs subgroup, erenumab)

Item	Full trial population (ITT)			3+ treatment failures		
	Erenumab 140 mg	Placebo	OR(95% CI)	Erenumab 140 mg	Placebo	OR (95% CI)
	n/N(%)	n/N(%)		n/N(%)	n/N(%)	
Any AE	88/188 (46.81)	110/282 (39.01)	1.38 (0.95, 2.00)	39/65 (60.00)	42/98 (42.86)	2.00 (1.06, 3.78)
Any SAE	2/188 (1.06)	7/282 (2.48)	0.42 (0.09, 2.06)	0/65 (0.00)	3/98 (3.06)	0.21 (0.01, 4.1)
AE resulting in discontinuation	2/188 (1.06)	2/282 (0.71)	1.51 (0.21, 10.78)	0/65 (0.00)	1/98 (1.02)	0.5 (0.02, 12.37)

AE= adverse event CI = confidence interval; OR=odds ratio; N = population NA=not reported; SAE= serious adverse event;
Source: Ashina et al 2018[3], Study 295

6.21 A comparison of safety outcomes for erenumab 140 mg and placebo based on the overall trial population are provided in the table below.

Table 10: Safety outcomes in Study 295 – erenumab vs. BSC

Outcome	Erenumab 140 mg (N=188) n (%)	Placebo (N=282) n (%)	RR (95% CI)	RD (95% CI)
Any AE	88 (46.8%)	110 (39.0%)	1.20 (0.97, 1.48)	0.08 (-0.01, 0.17)
SAE	2 (1.1%)	7 (2.5%)	0.43 (0.09, 2.04)	-0.01 (-0.04, 0.01)
AE resulting in discontinuation	2 (1.1%)	2 (0.7%)	1.50 (0.21, 10.56)	0.00 (-0.01, 0.02)
Death	0 (0%)	0 (0%)	-	-
Treatment-emergent AEs in ≥ 2% patients				
Injection site pain	7 (3.72%)	3 (1.06%)	3.5 (0.92, 13.36)	0.03 (0.0, 0.06)
Upper respiratory tract infection	6 (3.2%)	4 (1.4%)	2.25 (0.64, 7.87)	0.02 (-0.01, 0.05)
Nausea	6 (3.2%)	7 (2.5%)	1.29 (0.44, 3.77)	0.01 (-0.02, 0.04)
Nasopharyngitis	3 (1.6%)	16 (5.7%)	**0.28 (0.08, 0.95)**	**-0.04 (-0.07, -0.01)**
Constipation	8 (4.3%)	1 (0.4%)	**12.00 (1.51, 98.16)**	**0.04 (0.01, 0.07)**
Muscle spasms	7 (3.7%)	4 (1.4%)	2.63 (0.78, 8.84)	0.02 (-0.01, 0.05)
Migraine	5 (2.7%)	3 (1.1%)	2.50 (0.60, 10.34)	0.02 (-0.01, 0.04)
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Injection site erythema	[redacted]	[redacted]	[redacted]	[redacted]
Rhinitis	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse event; CI=confidence interval; RR=relative risk; RD=risk difference; SAE=serious adverse event; **bold**=statistically significant
Source: Table 2.28 and Table 2.29, p66 of the resubmission

6.22 The overall trial comparisons indicated statistically significantly more frequent occurrence of constipation and injection site erythema in erenumab-treated patients compared with those treated with placebo. Nasopharyngitis occurred statistically significantly more frequently in placebo-treated patients.

6.23 While the specific AEs presented in the resubmission were treatment-emergent AEs, the resubmission did not provide any data for treatment-related AEs. The TGA clinical evaluation report (CER) provided a summary of drug-related adverse events across the

[3] Ashina M, Tepper S, Brandes JL, Reuter U et al. Efficacy and safety of erenumab (AMG334) in chronic migraine patients with prior preventive treatment failure: A subgroup analysis of a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2018; 38(10): 1611-1621

pooled erenumab trials 295, 296, 178 and 297. These trials included chronic and episodic migraine patients. Drug-related AEs were defined as those that occurred with ≥1% overall incidence in either the 70 mg or 140 mg groups and with ≥2 times the rate of the placebo group. For the pooled data injection site reactions, constipation, pruritus and muscle spasms were defined as drug-related AEs.

6.24 The resubmission did not addressed the potential cardiovascular risk associated with erenumab. Robbins (2018)[4] noted that CGRP may be helpful in preventing cardiovascular disease but when the protective effects of CGRP are diminished it is possible that cardiac or cerebral infarcts may become more severe. MaassenVanDenBrink (2018)[5] considered that appropriate studies assessing the safety of blocking the effects of calcitonin gene-related peptide (CGRP) are lacking and the risk may be different in women (who make up the majority of migraine sufferers) compared to men. The ESC noted that Study 295 excluded patients with known cardiovascular disease or uncontrolled hypertension and the risks of erenumab in this population are not known.

Comparative harms – erenumab v. Botox

6.25 As for the July 2018 submission, the resubmission provided only an indirect comparison of the overall trial populations for safety outcomes. The resubmission stated that AEs were not reported for the subgroup in the Botox trials, hence no indirect comparison was possible for that subgroup population.

6.26 The resubmission provided the same grouped safety outcomes as presented in the July 2018 submission: any AE; SAE; AEs resulting in discontinuation; and death. The resubmission also presented an additional outcome, injection site pain, as data for this outcome was available in the publication of the pooled Botox trials. Results of the comparisons are provided below.

Table 11: Results of the indirect comparisons between erenumab and Botox for safety outcomes – overall trial population

	n with event/N (%)		OR	n with event/N (%)		OR	Indirect OR (95% CI)
Outcome	**Erenumab 140 mg**	**Placebo**		**Botox**	**Placebo**		
Any AE	88/188 (46.81%)	110/282 (39.01%)	1.38 (0.95, 2.00)	429/687 (62.45%)	358/692 (51.73%)	1.55 (1.25, 1.92)	0.89 (0.58, 1.37)
SAE	2/188 (1.06%)	7/282 (2.48%)	0.42 (0.09, 2.06)	33/687 (4.8%)	16/692 (2.31%)	2.13 (1.16, 3.91)	0.20 (0.04, 1.06)
Discontinuation due to AE	2/188 (1.06%)	2/282 (0.71%)	1.51 (0.21, 10.78)	26/687 (3.78%)	8/692 (1.16%)	3.36 (1.51, 7.48)	0.45 (0.05, 3.76)
Death due to AE	0/188 (0%)	0/282 (0%)	-	0/687 (0%)	0/692 (0%)	-	-
Injection site pain	7/188 (3.72%)	3/282 (1.06%)	3.6 (0.92, 14.09)	22/687 (3.2%)	14/692 (2.02%)	1.6 (0.81, 3.16)	2.25 (0.49, 10.34)

AE=adverse event; CI=confidence interval; OR=odds ratio; SAE=serious adverse events
Source: Table 2.41, p80 of the resubmission.

[4] Robbins L. CGRP antagonists: Physiologic effects and serious side effects. *Headache* 2018; 58(9): 1469-71.
[5] MaassenVanDenBrink A, Rubio-Beltran E, Duncker D, Villalon CM. Is CGRP receptor blockade cardiovascularly safe? Appropriate studies are needed. *Headache* 2018; 58(8): 1257-58.

6.27 There were no statistically significant differences between erenumab and Botox for the occurrence of any of the grouped outcomes or injection site pain. As noted above, the comparisons presented by the resubmission were based on the overall trial population and it cannot be assumed the observed results will apply to the nominated subgroup which corresponds to the proposed PBS population. The PBAC also noted the transitivity issues (paragraph 6.18) across the trials which may impact on assessing the comparative safety of erenumab and Botox.

6.28 The PSCR provided an indirect comparison of an additional 6 adverse events that were reported in a publication of the pooled Botox trials (Dodick 2010[6]) and for which there were data available for erenumab (see Table 12 below). The PSCR stated the analysis demonstrated similar occurrences of the 6 AEs between erenumab and Botox with a trend of erenumab having less AEs.

[6] Dodick DW, Turkel CC, DeGryse RE, Aurora SK et al. Onabotulinumtoxin A treatment reduce headache duration in adults with chronic migraine: Pooled results from the double-blind, randomized, placebo-controlled phase of the PREEMPT clinical program. Headache 2010; 50: 58-59

Table 12: Indirect comparison in total trial population (erenumab vs Botox)

	Erenumab			Botox			Indirect
	Erenumab 140 mg n/N(%)	Placebo n/N(%)	OR (95% CI)	Botox n/N(%)	Placebo n/N(%)	OR (95% CI)	OR (95% CI)
Neck Pain	[redacted]/1.88 ([redacted])	[redacted]/282 ([redacted])	([redacted], [redacted])	46/687 (6.7)	15/692 (2.17)	3.24 (1.79, 5.86)	([redacted], [redacted])
Muscular weakness	[redacted]/188 ([redacted])	[redacted]/282 ([redacted])	[redacted] ([redacted], [redacted])	38/687 (5.53)	2/692 (0.29)	20.2 (4.85, 84.07)	[redacted]
Musculoskeletal pain	[redacted]/188 ([redacted])	[redacted]/282 ([redacted])	[redacted] ([redacted], [redacted])	15/687 (2.18)	5/692 (0.72)	3.07 (1.11, 8.49)	[redacted] ([redacted], [redacted])
Headache	[redacted]/188 ([redacted])	[redacted]/282 ([redacted])	[redacted] ([redacted], [redacted])	20/687 (2.91)	11/692 (1.59)	1.86 (0.88, 3.9)	[redacted] ([redacted], [redacted])
Myalgia	[redacted]/188 ([redacted])	[redacted]/282 ([redacted])	[redacted] ([redacted], [redacted])	18/687 (2.62)	2/692 (0.29)	9.28 (2.15, 40.16)	[redacted] ([redacted], [redacted])
Musculoskeletal stiffness	[redacted]/188 ([redacted])	[redacted]/282 ([redacted])	[redacted] ([redacted], [redacted])	16/687 (2.33)	5/692 (0.72)	3.28 (1.19, 8.99)	[redacted] ([redacted], [redacted])

Note: 1 erenumab study 295 vs Botox pooled results
CI = confidence interval; OR=odds ratio; AE= adverse event; SAE= serious adverse event; NA=not reported.
Source: Study 295, Dodick 2010

Benefits/harms

6.29 On the basis of the direct evidence presented by the submission (see Tables 6 and Table 10 above), for every 100 patients treated with erenumab 140 mg in comparison to BSC and over a duration of follow-up of 12 weeks:

- Approximately 23 more patients would have ≥50% reduction in monthly migraine days.
- Approximately 4 fewer patients would have nasopharyngitis.
- Approximately 4 more patients would have constipation.
- Approximately 3 more patients would have injection site erythema (redness).

6.30 Over a 12 week time period, patients treated with erenumab 140 mg would experience an average reduction of approximately 4.2 migraine days per month compared to patients treated with BSC.

6.31 On the basis of the indirect evidence presented by the submission (see Tables 7 and 11 above) the comparison of 12 weeks of erenumab 140 mg and 24 weeks of Botox resulted in:

- No difference in the reduction of monthly headache days.
- No difference in the proportion of patients with ≥50% reduction in monthly headache days.
- No difference in the number (but different types) of AEs, SAEs, or cases of injection site pain.

Clinical claim

6.32 Based on the direct comparison of erenumab and BSC, the resubmission described erenumab as superior in terms of comparative effectiveness and equivalent in terms of comparative safety compared to BSC.

6.33 Based on the indirect comparison of erenumab and Botox, the resubmission described erenumab as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety.

6.34 The PBAC considered that the claim of superior comparative effectiveness compared to BSC was reasonable but considered the magnitude of the benefit was highly uncertain. The PBAC considered the claim that erenumab has equivalent safety to BSC to also be not adequately supported.

6.35 The PBAC considered that the claim of non-inferior comparative effectiveness and safety compared to Botox was not adequately supported by the data.

6.36 The PBAC noted the clinical claims in the submission were based on clinical data from a small (34%) subgroup of patients in the pivotal clinical study and were only based on the 140 mg dose of erenumab.

6.37 The PBAC noted no clinical data were presented in the resubmission for the 70 mg dose of erenumab for either the ITT or subgroup population.

6.38 The PBAC noted the resubmission did not nominate a non-inferiority margin for the indirect comparison versus Botox and considered the lack of statistically significant difference does not adequately establish non-inferiority.

Economic analysis

6.39 The resubmission presented a cost-utility analysis (CUA) based on the within trial comparison of erenumab and BSC and a cost-minimisation analysis (CMA) based on the indirect comparison versus Botox.

Cost utility analysis

6.40 The economic model in the July 2018 submission was based on a superiority claim versus Botox. The PBAC and ESC had raised a number of points regarding the economic evaluation presented in the July 2018 submission. A summary of those points along with the resubmission's response is provided in the table below.

Table 13: PBAC and ESC comments on the July 2018 economic model

	Comment	Resubmission response
Efficacy outcome	• The efficacy outcome (50% responder rate based on the indirect comparison of erenumab and Botox) did not reach statistical significance and it was not valid to include in model (paragraph 6.45 PSD; paragraph 6.25 ESC Advice).	• The comparator revised to BSC. The advantage for erenumab over placebo was statistically significant for the outcome of 50% responder rate.
Duration of response	• The model assumed that responders will maintain response for the duration of the economic model (5 years), unless they die or discontinue. The submission did not provide any evidence to support maintenance of response. (paragraph 6.46 PSD; paragraph 6.25 ESC Advice)	• The resubmission cited evidence from the open-label extension trial Study 255 to support maintenance of response.
Discontinuation	• The rates of discontinuation were sourced from results of the overall trial population and not the proposed PBS population, with no discussion of the applicability of these results to the proposed PBS population. (paragraph 6.47 PSD; paragraph 6.25 ESC ADV)	• Rates of discontinuation continued to be sourced from the overall trial population on the basis that subgroup data were not available. The resubmission conducted sensitivity analyses for discontinuation.
Utility values	• Severity of headache was not factored into the model, despite the fact that it can have a large impact on utility as shown by Stafford (2012)[7]. (paragraph 6.48 PSD; paragraph 6.25 ESC Advice). • The ESC noted that there are other sources of utilities that could be used to increase the validity of the modelling, such as Brown et al (2008)[8]. (paragraph 6.53 PSD; paragraph 6.26 ESC ADV)	• Severity of headache was not included in the determination of utility values for the model. • While utility values were altered due to the changes made in calculation of MMD distributions, values were still sourced from MSQ results from Study 295 and no alternate utility sources were considered by the resubmission.
Resource use	• The ESC advised that the potential financial and effectiveness impact of self-administration and wastage was worth consideration. (paragraph 6.49 PSD; paragraph 6.25 ESC ADV) • Maintenance healthcare resource usage was based on data from a European study which was likely to differ to the Australian context. (paragraph 6.50 PSD; paragraph 6.25 ESC ADV)	• No discussion of wastage and its potential impact was provided. • Maintenance healthcare costs remained based on the European study.
Use of MMD distributions	• MMD distributions were used to determine utility values and resource use. Baseline distributions included data for the 70 mg dose of erenumab. The economic model applied an assessment point of 24 weeks for responders however, the MMD distributions defined responders at 12 weeks. (paragraph 6.51 PSD; paragraph 6.25 ESC ADV)	• Distributions no longer include data from the 70 mg group. • The assessment timepoint in the model was changed to 12 weeks. • Distributions are based on subgroup and treatment-specific data.
Extrapolation	• The observed short-term (12 weeks or 3 months) benefit was assumed to be maintained on a last observation carried forward basis. (paragraph 6.54 PSD; paragraph 6.27 ESC ADV)	• The resubmission maintained the same approach to extrapolation, citing 52-week evidence from Study 255 to support maintenance of response.
Cost-effectiveness	• Erenumab would be cost-effective with an ICER between $15,000 - $45,000 per QALY, in line with the base case ICER of Botox for chronic migraine. (paragraph 7.20 PSD)	• Base case ICER of $[redacted].

ICER=incremental cost effectiveness ratio; MMD=monthly migraine days; MSQ=Migraine-specific Quality of Life Questionnaire; PSD=public summary document

Source: Compiled from Section 3.2 of the resubmission and 5.05.COM.61-78.

6.41 The resubmission changed the comparator in the modelled evaluation to BSC instead of Botox. As such, the comparison is now direct and erenumab has a statistically

significant advantage over the comparator for the modelled outcome of ≥50% responder rate. However, the PBAC considered the magnitude of benefit continues to be highly uncertain given the issues raised with the subgroup analysis.

6.42 The resubmission altered how the MMD distributions, which determine utility values and healthcare resource usage, are derived. The data used for the MMD distributions was subgroup-based and excluded the erenumab 70 mg dose. The ESC previously raised that the distributions applied in the July 2018 model were implausible (paragraph 6.25 July 2018 ESC Advice). The revised MMD distributions remained implausible, as there were unrealistically high MMDs for responders, as well as values of 28 MMDs for a small proportion of responders and close to 30% of responders with just one MMD. The ESC and PBAC considered the differences in the MMD distributions for erenumab and BSC for both responders and non-responders lacked validity including that erenumab non-responders have slightly fewer MMD days than BSC non-responders.

6.43 The resubmission applied the same sources for discontinuation rates (Study 295 and Study 255) as used in the July 2018 submission and maintained the assumption that response observed at 12 weeks would be maintained for the duration of the model (5 years).

6.44 The table below provides a summary of the model structure.

Table 14: Summary of model structure and rationale

Component	Summary
Time horizon	5 years in the model base case vs. 12 weeks in the erenumab trial.
Outcomes	Quality-adjusted life years (QALYs).
Methods used to generate results	Markov cohort analysis.
Health states	Responder; Non-responder; In response/on treatment; Discontinued due to poor response; Discontinued due to adverse events; Dead.
Cycle length	3 months with half cycle correction.
Transition probabilities	Study 295

Source: Source: Table 3.6, p99 of the resubmission.

6.45 A summary of the key drivers of the economic model is provided in the table below.

[7] Stafford MR, Hareendran A, Ng-Mak DS, Insinga RP et al (2012). EQ-5D™-derived utility values for different levels of migraine severity from a UK sample of Migraineurs. *Health Qual Life Outcomes* 2012; *10:65.*

[8] Brown JS, Neumann PJ, Papadopoulos G, Ruoff G, Diamond M, Menzin J. Migraine frequency and health utilities: findings from a multisite survey. *Value Health* 2008; 11(2): 315-21.

Table 15: Key drivers of the model

Description	Method/Value	Impact
Clinical evidence	There were inconsistencies in the data applied to the model, with efficacy data sourced from the subgroup population of Study 295 while discontinuation rates and adverse events were sourced from the overall trial population. In addition, evidence from Study 295 may not accurately reflect the effectiveness of erenumab in clinical practice. As noted by the ESC for the July 2018 submission, Study 295 excluded patients with psychiatric comorbidities which have been found to be prevalent with chronic migraine[9] The efficacy data from the subgroup was not adequately supported.	Moderate, favours erenumab
Parametric distributions	As for the July 2018 model, the current model is structured so that cost and utility values for each monthly migraine day (MMD) frequency are calculated and then weighted according to a predicted MMD distribution, generating mean values for that health state. The resubmission revised the determination of the MMD distributions so that data was sourced from the subgroup population of Study 295 and data for patients using the 70 mg dose was excluded. Even with these alterations the distributions produced remained implausible, including unrealistically high MMDs for responders, as well as values of 28 MMDs for a small proportion of responders and close to 30% of responders with just one MMD, plus differential distribution of MMDs for responders and non-responders in the two different arms. This lack of accuracy in the distributions will be reflected in the utility values and resource usage and cost values applied in the economic model	Moderate, favours erenumab
Extrapolation	The resubmission has maintained the same approach to extrapolation in the revised model, with extrapolation of the clinical data performed on a last observation carried forward basis. As such, patients who are identified as responders at the 12 week assessment point maintain that response for the duration of the model, although they are subject to risk of treatment discontinuation due to AEs or death. The resubmission cited data from Study 255 to support the continued approach to extrapolation however these data were based on a small number of 140 mg-treated patients ([redacted]) and only extended to 52 weeks, with no quantification of response over a longer time period. The ESC advised that the extrapolation in the model is very favorable and based on limited evidence.	High, favours erenumab
Utility values	The resubmission has not addressed the point made by the PBAC and ESC that severity of headache was not factored into the model despite evidence showing it can have a large impact on utility. The resubmission has also not provided any discussion around other sources of utility values. The PBAC and ESC had cited Brown (2008), a paper which looked at migraine frequency and utility which would be particularly relevant in the case of chronic migraine and could have been used as a source for sensitivity analysis.	Moderate, favours erenumab.

Source: Compiled from Section 3.2 of the resubmission and July 2018 PSD.

6.46 The results of the economic evaluation are provided in the table below.

[9] Teixeira AL, Costa EAC, da Silva, AA. Psychiatric comorbidities of chronic migraine in community and tertiary care clinical samples. *J Headache Pain* 2012; 13: 551-55.

Table 16: Results of the stepped economic evaluation

Steps	Incremental cost	Incremental effectiveness	ICER
1: Trial-based analysis versus BSC			
1a: Successful response in overall trial population (41.2% for erenumab versus 23.5% for placebo for monthly migraine days).	$[redacted]	17.7% (41.2%-23.5%)	$[redacted] per additional responder at 12 weeks
1b: Successful response in proposed PBS population ([redacted]% for erenumab versus [redacted]% for placebo for monthly migraine[a] days).	$[redacted]	23.2% (38.5%-15.3%)	$[redacted] per additional responder at 12 weeks
2: Modelled analysis versus BSC (subgroup population)			
2a: 6 months duration	$[redacted]	[redacted]	$[redacted]/QALY
2b: 1 year duration	$[redacted]	[redacted]	$[redacted]/QALY
2c: 3 years duration	$[redacted]	[redacted]	$[redacted]/QALY
2d: 5 years duration (base case)	**$[redacted]**	[redacted]	**$[redacted]/QALY**

[a] Table 3.30 of the resubmission (p128) had labelled this outcome as monthly headache days however the values used were for monthly migraine days.

BSC=best supportive care

Source: Table 3.30, p128 of the resubmission.

The redacted table shows ICERs per QALY in the range of $15,000 to $200,000.

6.47 The base case ICER versus BSC in the resubmission was not likely to accurately represent the cost-effectiveness of erenumab, given the following:

- While the basis of the MMD distributions used to determine resource usage costs and utility values were modified to be sourced from Study 295 subgroup data, the plausibility of the distributions remained questionable. There were unrealistically high MMDs for responders, as well as values of 28 MMDs for a small proportion of responders and close to 30% of responders with just one MMD.
- The evidence cited by the resubmission to support ongoing maintenance of response with erenumab (Study 255) did not adequately demonstrate the maintenance of benefit. The open-label extension study was designed to assess occurrence of AEs and did not assess treatment effect over time. In addition, the number of patients in the 140 mg dose group was small ([redacted]) and data were available for only one year.
- The resubmission continued to apply rates of discontinuation sourced from the overall trial population and Study 255 rather than the subgroup population.
- The clinical evidence upon which the revised model was based (proportion of patients with ≥50% reduction in MMDs in the subgroup of Study 295) may not accurately reflect the effectiveness of erenumab in clinical practice.
- The ESC noted no costs associated with the administration of erenumab were included in the model and considered it may be appropriate to include some costs (i.e., an initial clinician visit to learn how to self-administer and wastage associated with self-administration).

6.48 The ESC noted a number of concerns regarding the utilities included in the model:

- Utilities were mapped from the Migraine Specific Quality of Life Questionnaire (MSQ) data collected in Study 295 to UK-5D values using a published algorithm.

However, it was unclear whether the MSQ data from Study 295 was based on the overall trial population or the nominated subgroup.

- The resubmission did not consider the severity of headache in its determination of utility values, even though it has been shown to have a large impact on utility[10]. The PSCR stated incorporating severity of headache would be an unnecessary complication of the model.
- Alternative sources of utilities that could have been used in the model, or in sensitivity analyses, were not discussed in the submission.

6.49 The model estimated an average incremental reduction of [redacted] migraine days over 5 years, which equates to approximately [redacted] less migraine days per month for erenumab-treated patients. This was less than the reduction of approximately 4.2 migraine days per month over 12 weeks observed in Study 295 for erenumab-treated patients. The PBAC noted that although the average number of migraine days avoided per month appeared consistent with the trial, the assumed distribution of MMDs seems implausible.

Cost minimisation analysis

6.50 The resubmission presented a cost-minimisation analysis applying equi-effective doses of erenumab 140 mg every 4 weeks = Botox 195U every 12 weeks.

6.51 The PBAC considered a cost-minimisation analysis may not be appropriate as non-inferiority was not supported with the data presented in the resubmission.

Drug cost/patient/year

6.52 The table below provides a summary of annual treatment costs for erenumab. Results for the July 2018 submission are provided for comparison. The resubmission provided an estimate of costs without the proposed continuation rule (≥50% response required to continue treatment) which assumed 13 doses of erenumab over a year (DPMQ of $[redacted] per dose) resulting in an annual cost of $[redacted]. With the continuation rule applied the cost over a year using response assessment was $[redacted].

[10] Stafford MR, Hareendran A, Ng-Mak DS, Insinga RP et al (2012). EQ-5D™-derived utility values for different levels of migraine severity from a UK sample of Migraineurs. *Health Qual Life Outcomes* 2012; *10:65.*

Table 17: Annual treatment costs per patient for erenumab – resubmission and July 2018 submission

	Resubmission	July 2018 submission
Annual cost with assuming no response assessment		
Drug cost per dose (DPMQ)	$	$
Number of treatment cycles (1 cycle=4 weeks)	13	13
Total cost over 12 months	**$**	**$**
Annual cost with response assessment		
Response rate - Study 295 subgroup (versus Botox for July 2018)	38.50%	39.40%
Number of treatment cycles to response assessment at 12 weeks (24 weeks July 2018)	3	6
Number of treatment cycles post-assessment to 12 months	10	7
Cost over 12 months for with response assessment[a]	**$** [b]	**$** [c]

DPMQ=dispensed price for maximum quantity

[a] The PSCR acknowledged there was an error in this calculation in the resubmission. The corrected values are presented.

[b] $ =($ × 6) + (38.50% × 7 × $)

[c] $ =($ × 6) + (39.40% × 7 × $)

Source: Table 3.29, p128 of the resubmission.

6.53 The resubmission calculated the drug cost per patient per year based on the price of erenumab applied in the economic model (DPMQ of $ per dose). Applying the requested weighted price for erenumab (DPMQ of $ per dose), the drug cost/patient/year became $ based on response assessment at 12 weeks.

6.54 The estimated annual cost for a responder with response assessment at 12 weeks ($) relies on the response rate sourced from the erenumab subgroup in Study 295 and may not reflect the response rate in clinical practice.

6.55 The resubmission adopted a "weighted" approach to pricing based on a CUA of erenumab versus placebo and a CMA of erenumab versus Botox. The weighted price ($) was based on % of the higher price ($) used in the CUA and % of the cost-minimised price ($). The ESC and PBAC considered the weighted price for erenumab was highly dependent on the proportion of use between the two populations. The ESC and PBAC further considered a higher price for erenumab for the population not currently treated with Botox compared with those treated with Botox was not adequately justified in the resubmission.

Estimated PBS usage & financial implications

6.56 The resubmission was considered by the DUSC. The resubmission used an epidemiological approach to estimate the utilisation and financial implications associated with the requested PBS listing of erenumab for chronic migraine (Table 18).

Table 18: Estimated use and financial implications

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

[a] Assuming initiating patients will use 4.25 scripts per year and continuing patients will use 10.40 scripts per year.
[b] Assuming 13.04 scripts per year and for patients in their first year of treatment a half-year correction was applied (6.52 scripts).
Source: Table 14, 5.05.COM.20.

6.57 The overall estimated net cost to the Government for the first 6 years of erenumab listing was more than $100 million with an estimated total number of treated patients of over 200,000.

6.58 The resubmission considered the following patients:

- Botox patients:
  - Those who have failed Botox treatment.
  - Those currently treated with Botox who will switch to erenumab.
  - Patients who are naïve to Botox (annual initiators).
- Non-Botox (BSC) patients:
  - High-frequency triptan users.
  - Other patients diagnosed with chronic migraine who are treated by a GP.
  - Undiagnosed chronic migraine patients

<u>Botox populations</u>

6.59 The resubmission assumed growth in the non-Botox population but not the Botox population.

6.60 The DUSC considered the application of linear extrapolation was likely to overestimate the total Botox sub-populations.

6.61 The DUSC considered the estimated rate of uptake in the Botox switch and initiator populations were reasonable. For the Botox failure sub-population, the DUSC considered the number of eligible patients was slightly overestimated, as the method relied on assumptions in interpretation of initiations and discontinuations prior to the availability of PBS patient data for Botox, which may have double-counted patients who initiated prior to this period. DUSC also noted that the method did not account for any deaths or re-initiations.

Non-Botox (BSC) populations

6.62 The DUSC considered there is a high degree of unmet clinical need in the subgroup of patients considered to be high triptan users, particularly for those patients who have not used Botox for reasons such as cost or lack of specialist access. The DUSC considered the estimated uptake for this subpopulation to be slightly overestimated as access to or cost of a specialist visit will likely remain a barrier for some patients.

6.63 The DUSC considered the method for estimating the number of patients with chronic migraine managed by a GP that may be eligible for treatment with erenumab was uncertain and unreliable. Additionally, the DUSC considered there is potential overlap of GP-managed patients with the triptan user sub-population.

6.64 For the undiagnosed patients, the DUSC considered the applicability of the Headache Australia figure to estimate this sub-population is unclear, as it was based on US and European prevalence studies.

6.65 The DUSC acknowledged there is a high unmet need for some of the identified sub-populations but considered uptake is likely to be overestimated in the early years of the estimates due to the rate limiting steps of neurologist referral and the requirement for patients to have ≥3 prior treatment failures.

6.66 The DUSC considered continuation rates could be underestimated across all populations due to the following:

- Relative ease of access and administration of erenumab over Botox may mean that re-initiation and ongoing use could be higher than estimated;
- Partial responders may continue therapy as there is no proper tool to assess patient response;
- Some patients could be on treatment indefinitely for fear of rebound headaches if treatment is discontinued.

6.67 Overall, the DUSC considered the estimates of the eligible treated population presented in the submission to be overestimated.

Financial Management – Risk Sharing Arrangements

6.68 The resubmission stated that if the PBAC recommends erenumab for chronic migraine the sponsor was willing to share the risk of uncertainty in the estimates and to

negotiate expenditure caps applicable specifically to erenumab. The resubmission provided no further detail on the potential risk-sharing arrangement (RSA).

Quality use of medicines

6.69 The ESC considered listing only a 140 mg dose of erenumab was not appropriate and is not consistent with the 'choosing suitable medicines' second principle of Australia's Quality Use of Medicines (QUM) strategy which requires consideration of the appropriate dose. The recommended dose of erenumab in the PI is 70 mg every four weeks with some patients benefiting from a dose of 140 mg every weeks. The DUSC considered listing only the 140 mg dose may create the potential for wastage and overtreatment.

6.70 The DUSC recalled its previous advice to consider a quality use of medicines strategy for GP training for continuing and discontinuing therapy, and recognition of medication overuse headache.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the Authority Required (Streamlined) listing of erenumab for the treatment of chronic migraine. The PBAC considered the magnitude of the clinical benefit, and the non-inferior efficacy claim versus Botox, were uncertain due to being based on a subgroup of the trial population and data for only the 140 mg dose. There were significant issues with the economic model, and the cost-effectiveness of erenumab versus BSC at the price proposed in the resubmission was highly uncertain. The expected financial impact of listing erenumab on the PBS was very high and uncertain.

7.2 The PBAC acknowledged there was a clinical need for effective medicines to treat chronic migraine and noted the consumer comments received for the July 2018 submission and the resubmission in support of a PBS listing. The PBAC noted the significant impact of migraine on quality of life and that the DUSC estimated approximately 400,000 patients may experience chronic migraine. Given the significant burden of disease and the high number of patients that may possibly benefit from treatment, the PBAC considered it was important to ensure any PBS listing was based on the best available data, was appropriately targeted to the right patients and was cost-effective in those patients.

7.3 The PBAC noted the resubmission requested listing for the 140 mg dose only and considered exclusion of the 70 mg dose from the resubmission was inappropriate and inconsistent with the recommended dose within the Product Information. The PBAC considered it was likely that a proportion of patients would be appropriately treated with the 70 mg dose rather than the 140 mg dose, but as no clinical data were presented in the resubmission, the clinical and economic impact of this is unknown. The PBAC noted the pre-PBAC response indicated that the 70 mg dose could also be listed on the PBS if that was the preference of the PBAC and provided some data for the 70 mg dose. The PBAC considered the data provided in the pre-PBAC response was

of limited use as it was not evaluated, did not include any safety data and did not include any data for the subgroup.

7.4 The PBAC considered that Botox and BSC are reasonable comparators. However, the PBAC did not consider the weighting across the comparators (21% Botox, 79% BSC) to be adequately supported. Further, the PBAC did not consider a differential price for the two groups of patients (those treated with Botox versus those not treated with Botox) to be adequately justified. The PBAC also noted that a proportion of patients may be treated with sequential use of erenumab and Botox.

7.5 The PBAC noted the clinical claims in the resubmission were based on a small subgroup (163/476, 34%) of patients in the pivotal study. The PBAC considered the use of a subgroup to support the clinical and economic comparisons to BSC and Botox was inadequately supported. The PBAC noted the subgroup analyses were not pre-specified and patients in the subgroup were not representative of the patients likely to be treated with erenumab should it be listed on the PBS (paragraph 6.10). The PBAC also recalled its previous advice that the use of data from a small subgroup of patients was insufficient given the potential to treat a large number of patients.

7.6 The PBAC noted erenumab decreased monthly migraine days (MMD) and a higher proportion of patients achieved a 50% reduction in MMD over 12 weeks of treatment compared to BSC, however considered the magnitude and clinical significance of the benefit was uncertain. The uncertainty was increased by the lack of data provided for the 70 mg dose.

7.7 The PBAC considered there were significant transitivity issues with the indirect comparison to Botox. The PBAC recalled the previous ESC advice that given the substantial differences in responses observed in the placebo arms of Study 295 and the PREEMPT studies, an indirect comparison was likely to be invalid. The PBAC noted the issues raised during the July 2018 consideration of erenumab had not been adequately addressed in the resubmission.

7.8 Notwithstanding the issues discussed in paragraph 7.7, the resubmission did not nominate a non-inferiority margin and the PBAC considered the lack of statistically significant difference between erenumab and Botox for the indirect comparison does not adequately establish non-inferiority.

7.9 The PBAC noted the ESC advice that there were significant issues with the economic model and, in addition to the uncertainty of the clinical benefit in the subgroup population, considered it was of limited value in determining the cost-effectiveness of erenumab. The economic model applied MDD distributions that were not plausible, assumed ongoing maintenance of response to erenumab and applied utilities that were not adequately justified (paragraph 6.45 and 6.46). The ESC and PBAC considered the differences in the MMD distributions for erenumab and BSC for both responders and non-responders lacked validity including that erenumab non-responders have slightly fewer MMD days than BSC non-responders.

7.10 The PBAC noted the resubmission proposed a price for the comparison versus BSC that was higher than the proposed price for the comparison versus Botox. The PBAC

considered a higher erenumab price in the population of patients currently treated with BSC was not adequately justified in the resubmission. The PBAC noted the majority of use of erenumab was expected in the BSC population and considered the request for a higher price in this population may be unreasonable. The resubmission provided no discussion of the differential value of erenumab across the two populations.

7.11 The PBAC noted a high proportion of expected use is in patients currently treated with BSC and the value of erenumab in this large group of patients is highly uncertain. The PBAC considered the issues with the economic model need to be addressed to support the value of erenumab in these patients.

7.12 The PBAC noted the overall estimated net cost to the Government for the first 6 years of erenumab listing was more than $100 million with an estimated total number of treated patients of over 200,000. The PBAC considered the financial estimates to be very high and uncertain. The PBAC considered there is the potential for high uptake of erenumab given the poor tolerability of available treatments and a high continuation rate given the subjective nature of the continuation criteria. Further, the risk of use outside the restriction criteria is significant.

7.13 The PBAC considered that any resubmission would need to be a major submission and would need to address the following issues:

- Propose a restriction criteria that addresses the issues raised in Section 2.
- Present all available efficacy and safety data for the doses recommended in the Product Information (PI). If the clinical claim is based on a subgroup of patients, the rational should be clearly supported with reference to Section 2.6.1 of the PBAC Guidelines. Any proposed equi-effective doses should take into account the doses recommended in the PI.
- Provide any further data that may be available to support the long term safety and benefit of erenumab at the recommended doses. The PBAC considered any data on the impact of treatment withdrawal would be informative.
- Address the issues regarding the economic model to support the cost-effectiveness of erenumab versus BSC.
- Propose a risk share arrangement to manage the uncertain patient population and the high overall financial impact.

7.14 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about

the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor had no comment.