

## 5.05 ERENUMAB, Injection 70 mg in 1 mL single dose pre-filled pen, Aimovig®, Novartis Pharmaceuticals Pty Ltd

### 1 Purpose of Application

- 1.1 The submission 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 and are also naïve to treatment with botulinum toxin type A (Botox). Erenumab has not been previously considered by the PBAC.
- 1.2 The submission requested listing on the basis of a cost-utility analysis compared to Botox. The key components of the clinical issue addressed by the submission are presented in Table 1.

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

Component	Description
Population	Adults with chronic migraine.
Intervention	Erenumab; 140 mg administered once every 4 weeks as a subcutaneous injection.
Comparator	Botox; administered by injection every 12 weeks to 31-39 sites in the head.
Outcomes	Change from baseline in the number of monthly migraine days; proportion of responders ( $\geq 50\%$ change from baseline); overall safety outcomes. The key outcome used in the submission's indirect comparison and economic model, the proportion of patients with at least 50% change from baseline in monthly headache days, was not reported as a primary, secondary or exploratory outcome in the pivotal erenumab trial.
Clinical claim	In adult patients with chronic migraine, erenumab is superior in terms of comparative effectiveness at reducing monthly headache days and non-inferior in terms of comparative safety to botulinum toxin type A.

Source: Table 1.1, p2 of the submission.

### 2 Requested listing

- 2.1 To allow general practitioners to prescribe continuing therapy, as requested in the submission, the Secretariat proposed two restrictions for erenumab: initial and continuing treatment phases. The proposed continuing restriction would not mandate prescribing to neurologists only. The Pre-Sub-Committee Response (PSCR) did not oppose this change.
- 2.2 The Secretariat's suggested additions are in italics and deletions are in strikethrough.

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
Erenumab, 70 mg/ mL, 2x1 mL, injection devices	1	5	\$ [REDACTED]	Aimovig® Novartis Pharmaceuticals

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Chronic
<b>Severity:</b>	-
<b>Condition:</b>	Migraine
<b>PBS Indication:</b>	Chronic migraine
<b>Treatment phase:</b>	<i>Initial</i>
<b>Restriction Level / Method:</b> Section 85 <i>Authority required</i>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Must be prescribed by a neurologist.
<b>Clinical criteria:</b>	<p>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 erenumab,</p> <p>AND</p> <p>Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with erenumab,</p> <p>AND</p> <p><del>Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of headache days per month after six treatment cycles (24 weeks duration) in order to be eligible for continuing PBS-subsidised treatment,</del></p> <p>AND</p> <p>Patient must be appropriately managed by his or her practitioner for medication overuse headache, prior to initiation of treatment with erenumab,</p> <p>AND</p> <p>Patient must not have <i>received prior treatment with</i> <del>had previous exposure to</del> botulinum toxin type A <i>for this condition</i></p> <p><del>Not used in combination with botulinum toxin type A</del></p>
<b>Population criteria:</b>	<p>Patient must be aged 18 years or older.</p> <p><del>Prophylactic migraine medications are propranolol, amitriptyline, methsergide, pizotifen, cyproheptadine or topiramate.</del></p>
<b>Prescriber Instructions</b>	<i>Prophylactic migraine medications are propranolol, amitriptyline, methsergide, pizotifen, cyproheptadine or topiramate.</i>
<b>Administrative Advice</b>	<i>This drug is not PBS-subsidised for use in combination with botulinum toxin type A</i>

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<b>Note</b>	<p>Continuing therapy only  <del>For prescribing by general practitioners as subsequent continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a neurologist.</del></p> <p>Applications for initial PBS-subsidised treatment for grandfather patients will provide for a maximum of 24 weeks of treatment. Approval will be based on the criteria included in the relevant restriction.</p>
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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
Erenumab, 70 mg/ mL, 2x1 mL, injection devices	1	5	\$ [REDACTED]	Aimovig® Novartis Pharmaceuticals

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Chronic
<b>Severity:</b>	-
<b>Condition:</b>	Migraine
<b>PBS Indication:</b>	Chronic migraine
<b>Treatment phase:</b>	<i>Continuing</i>
<b>Restriction Level / Method:</b> Section 85 <i>Authority required</i>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p><del>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 erenumab,</del>  AND  <del>Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with erenumab,</del>  AND  Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of headache days per month after six treatment cycles (24 weeks duration) in order to be eligible for continuing PBS-subsidised treatment;  AND  Patient must be appropriately managed by his or her practitioner for medication overuse headache, prior to initiation of treatment with erenumab.  AND  Patient must not have <i>received prior treatment with</i> <del>had previous exposure to</del> botulinum toxin type A <i>for this condition</i>  <del>Not used in combination with botulinum toxin type A</del></p>
<b>Population criteria:</b>	<p>Patient must be aged 18 years or older.</p> <p><del>Prophylactic migraine medications are propranolol, amitriptyline, methsergide, pizotifen, cyproheptadine or topiramate.</del></p>

<b>Administrative Advice</b>	<i>This drug is not PBS-subsidised for use in combination with botulinum toxin type A.</i>
<b>Note</b>	<p>Continuing therapy only  <del>For prescribing by general practitioners as subsequent continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a neurologist.</del></p> <p><del>Applications for initial PBS-subsidised treatment for grandfather patients will provide for a maximum of 24 weeks of treatment. Approval will be based on the criteria included in the relevant restriction.</del></p>

- 2.3 The requested restriction largely matched the PBS listing of Botox for chronic migraine, with two key differences: i) a patient must not have had previous exposure to Botox; and ii) erenumab must not be used in combination with Botox.
- 2.4 The Drug Utilisation Sub-Committee (DUSC) noted that the need for patients to be naïve to Botox has not been justified and may not be able to be applied in practice, therefore there is potential for use of erenumab outside the requested restriction in patients who have previously been treated with Botox. The Economics Sub-Committee (ESC) agreed that this was clinically reasonable to try erenumab if Botox treatment had failed.
- 2.5 The criterion that erenumab must not be used in combination with Botox is appropriate given absence of clinical evidence addressing the use of the two agents in combination. Should erenumab be PBS listed, a corresponding statement would need to be added to the Botox PBS listing, i.e. that it should not be used in combination with erenumab. The ESC noted that under the proposed restrictions for erenumab and the current restriction for Botox, clinicians would be likely to try erenumab but could still prescribe Botox in those with inadequate response to erenumab.
- 2.6 Another difference compared with the current Botox listing is that the requested restriction allows for prescribing of continuing therapy by a GP. The submission stated that this would reduce waiting time relevant to continuing therapy. The submission cited a 9 month waiting time for appointments with a neurologist, sourced from market research commissioned by the sponsor. This estimate of the waiting period was based on limited evidence, and was not likely to represent all patients. The PSCR reiterated that limiting prescribing to specialists would be at the expense of patient accessibility, particularly in the context of rural, regional and remote patients.
- 2.7 DUSC considered neurologist initiation of erenumab is appropriate, given its positioning at the end of the treatment algorithm. DUSC recalled that a subset of neurologists prescribe botulinum toxin. There were 609 neurologists that prescribed at least one PBS prescription of any drug in 2016, and 156 (25.6%) of these

prescribed botulinum toxin for chronic migraine.<sup>1</sup> DUSC considered it possible that a higher proportion of neurologists might prescribe erenumab, which may drive higher uptake than anticipated. In regards to the proposed prescribing by GPs, DUSC noted that the restriction therefore does not require a neurologist to assess the response to erenumab at any point. While DUSC noted that this would enhance access to ongoing treatment for people who may have difficulty accessing a neurologist, DUSC expressed concern that this may lead to indefinite continuation in patients who may not have achieved and maintained the necessary reduction in headache days. DUSC noted that some patients in the erenumab trial did not achieve and maintain a response. DUSC also noted that the potential for GP continuation would potentially provide capacity for neurologists to initiate more patients, since they would not be required to assess continuation.

- 2.8 The ESC noted the criterion ‘Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications prior to commencement of treatment with erenumab’. While a similar criterion is in the Botox restriction, the ESC and DUSC considered that the prior agents are poorly tolerated and so a significant proportion of patients with chronic migraine would meet this criterion. Furthermore, the ESC considered that a significant proportion of patients with three treatment failures may have a component of medication overuse headache contributing to their symptoms. DUSC considered that medication overuse headache is not well recognised and noted that it can be a side effect of migraine medication. DUSC considered this may be difficult to manage in practice, given the overlap between migraine and medication overuse headache. DUSC also noted the TGA delegate’s overview, which stated that “for subjects with chronic migraine and medication overuse the mean extent of benefit was similar to that of the overall chronic migraine population.”
- 2.9 The ESC noted that assessment of response could be subjective, and that the continuation rates for Botox were much higher (71%) than the response rates in the clinical trials for Botox (33%) (June 2017 DUSC report). The impact of assessment by a GP rather than a specialist on this assessment is not known.
- 2.10 The PSCR also stated that following the lodgement of this submission, the sponsor had been approached by pain/headache specialists practising in headache clinics who expressed an interest in initiating treatment for chronic migraine alongside neurologists. Unlike Botox, which requires neurologists to undertake certified injection training, erenumab is available as self-injected therapy, thus the PSCR requested that the PBAC to consider whether erenumab could be prescribed by pain/headache specialists with Fellow of the Royal Australasian College of Physicians (FRACP) and Fellowship of the Faculty of Pain Medicine, Australian and New Zealand

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<sup>1</sup> Department of Health. Botulinum toxin type A for chronic migraine: 24-month predicted versus actual analysis. Canberra: Department of Health; 2017. Available from the [PBS website](#).

College of Anaesthetists (FFPMANCA) accreditations for initial therapy. The impact increasing the number of prescribers would have on the number of patients initiating on erenumab is unknown.

- 2.11 While the use of the 24 week time point for assessment of response to determine continuing treatment corresponded to the Botox PBS listing, the trial evidence used to support the requested restriction assessed response at 12 weeks. The sponsor stated in its Pre-PBAC Response that it was willing to amend the requested restriction time point to 12 weeks to align with the trial instead of with the Botox listing.
- 2.12 The submission claimed that treatment response continues to improve for erenumab over time on the basis of evidence from an open-label extension trial, but only 10% of patients in the open-label extension trial used the erenumab dose in the requested restriction (140 mg).

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

### **3 Background**

#### **Registration status**

- 3.1 The submission was made under the TGA/PBAC parallel process. At the time of PBAC consideration, a positive Delegate's Overview, the sponsor's pre-Advisory Committee on Medicines (ACM) meeting response and a draft product information were available. Erenumab was registered on the Australian Register of Therapeutic Goods for the prophylaxis of migraine in adults on the 2<sup>nd</sup> of July, 2018.
- 3.2 The submission stated that erenumab has not received registration in any country at the time of submission, with the regulatory submissions to the EMA and FDA currently under review. The PSCR stated that erenumab was approved by the FDA for the preventative treatment of migraine in adults on 17 May 2018. The ESC noted that the recommended initial dose in the FDA approval was 70 mg for most patients. The TGA Delegate sought advice from the ACM on whether the available evidence supported a dose regimen of 70 mg QM with an increase to 140 mg QM only if there is an inadequate response. The updated draft product information provided with the sponsor's Pre-PBAC Response stated that some patients may benefit from a dosage of 140 mg, but the recommended dose is 70 mg.
- 3.3 The registration of erenumab includes both syringes and pre-filled pen (injection device), the sponsor confirmed that only the injection devices have been requested for listing in the current submission.

## Previous PBAC consideration

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

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

## 4 Population and disease

- 4.1 Migraine is 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 is adult patients with chronic migraine, defined as 15 or more headache days per month, at least 8 of which must be typical migraine days.
- 4.2 The submission stated that about half of the migraine population in Australia are chronic migraine sufferers. This was based on a literature review (Natoli 2010) which used the search dates 1999 to 2007 and selected 12 studies, conducted in the US, Brazil, Europe and Taiwan. As such, the proportion of chronic migraine sufferers reported by the submission was not Australia-based. Headache Australia has estimated that 345,800 adults in Australia have chronic migraine<sup>2</sup>, which represents approximately 1.4% of the total population and just over a tenth of the Australian population with migraine as identified by Stark (2007), which is considerably less than half of the population with migraine as claimed by the submission.
- 4.3 The submission stated that patients report substantial impairment in their ability to perform daily or physical activities, attend school/work and function socially (Munakata 2009; Linde 2012). Migraines are also associated with psychiatric and medical comorbidities such as depression, anxiety and vascular disorders (Bigal and Lipton 2009; Buse 2010). Medication overuse is also common, particularly in chronic migraine (Bussone 2010; Diener 2016).
- 4.4 Erenumab is a human monoclonal immunoglobulin (IgG2) which acts against the calcitonin gene-related peptide (CGRP) receptor. The requested restriction placed erenumab as a later-line therapy along with Botox, following failure of at least three prophylactic agents.

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

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<sup>2</sup> Sourced from: <http://headacheaustralia.org.au/migraine/chronic-migraine/>. This source also cites a chronic migraine fact sheet which states that the number of Australian adults with chronic migraine is approximately 450,000 or about 2% of the total population ([http://headacheaustralia.org.au/wp-content/uploads/2015/06/Chronic\\_Migraine\\_Fact\\_Sheet\\_FINAL.pdf](http://headacheaustralia.org.au/wp-content/uploads/2015/06/Chronic_Migraine_Fact_Sheet_FINAL.pdf)).

## 5 Comparator

- 5.1 The submission nominated Botox as the main comparator as it is the only prophylactic medication listed on the PBS for the treatment of chronic migraine in adult patients with refractory chronic migraine. The ESC agreed that the selection of Botox as a comparator was appropriate. However, both the ESC and DUSC noted that the use of Botox may be limited due to the need to see a neurologist for both prescription and administration, and that there would be eligible patients not currently treated with Botox who may take up erenumab due to the relative ease of administration and/or the potential to be continued by a GP.
- 5.2 DUSC also questioned, given the range of presentations of migraine, whether the population treated with Botox is the same as the population who would be treated with erenumab.
- 5.3 In addition, in practice it has been observed that Botox is frequently used with other prophylactic treatments (Stark et al., poster, at Australian and New Zealand Association of Neurologists 2017 Annual Scientific Meeting<sup>3</sup>) and there is a possibility that erenumab will also be used with other prophylactic medications. The TGA Delegate requested advice from ACM on concomitant administration of erenumab with other migraine prophylactic medications.

*For more detail 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 (1,886), health care professionals (24), and organisations (3) via the Consumer Comments facility on the PBS website. The comments described the physical, mental, and social impact of migraine on sufferers (including episodic and chronic migraine) and the inadequacy of other available treatments due to side effects, lack of effect, and, in the case of Botox, the 'horrific' pain associated with administration.
- 6.3 Many comments mentioned that erenumab is the first drug specifically designed for migraine prophylaxis – the Australian and New Zealand Headache Society (ANZHS) noted that erenumab "... potentially fills a significant gap in current therapeutics to combat migraine."

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<sup>3</sup> <http://dx.doi.org/10.1136/jnnp-2017-316074.60>

- 6.4 There were few comments from patients with experience with erenumab, with one comment describing reduced migraine symptoms and a significant improvement in quality of life due to erenumab.

### **Clinical trials**

- 6.5 The submission was based on an indirect comparison using one erenumab trial (Study 295; N=476) and two Botox trials (PREEMPT 1; N=679 and PREEMPT 2; N=705) with placebo as the common comparator. The submission also included data from Study 255, an open-label extension of Study 295. Given the substantial differences in the responses observed in the placebo arms of the trials, the ESC advised that this indirect comparison was likely to be invalid. This issue of differences between the response rates in the placebo arms was not addressed by the submission, but in its Pre-PBAC Response the sponsor stated that the odds ratios used to present the results of the indirect comparison would have included adequate adjustment for the different placebo response rates.
- 6.6 The indirect comparison was based on a post-hoc subgroup selected to correspond to the requested PBS restriction, patients who had failed  $\geq 3$  prophylactic medications and for erenumab, were naïve to Botox. For erenumab, where this level of prophylactic use was an exclusion criterion for Study 295, this subgroup comprised less than ■■■% of the Study 295 trial population. The Pre-PBAC Response explained that the inclusion of these patients despite the exclusion criterion was due to the definition of ‘failure’ of prophylactic medications being stricter for the post-hoc subgroup than for the entire trial.
- 6.7 The trials also excluded patients with psychiatric comorbidities, which Teixeira et al. (2012)<sup>4</sup> found to be prevalent with chronic migraine. The ESC advised that this exclusion could diminish the applicability of the results of this research to the PBS chronic migraine population to some extent.
- 6.8 Details of the trials presented in the submission are provided in the table below.

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<sup>4</sup> Teixeira, A L, Costa, E A C, da Silva, A A (2012). Psychiatric comorbidities of chronic migraine in community and tertiary care clinical samples. *The Journal of Headache and Pain* 13: 480

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Erenumab</b>		
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
<b>Botox</b>		
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 2.8, p20-24 of the submission.

6.9 The key features of the randomised trials included in the indirect comparison are provided in the table below. As the subgroup analysis presented by the submission formed the basis of the clinical claim, information relative to the subgroup is included in the table.

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

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Erenumab vs. placebo</b>						
Study 295	476 (subgrp=■ or ■ <sup>a</sup> )	R, DB, MC 12 weeks	Low	Failed ≥3 prophylactic medications and naïve to Botox	Change from baseline in monthly migraine days	≥50% responder for change in headache days; AEs
<b>Botox vs. placebo</b>						
PREEMPT I and PREEMPT II pooled analysis	1,384 (subgrp=396 or 479 <sup>a</sup> )	R, DB, MC 24 weeks	Low	Failed ≥3 prophylactic medications	Change from baseline in headache days	≥50% responder for change in headache days; AEs

<sup>a</sup> The size of the subgroups varied depending on the outcome assessed. For erenumab the analysis of change in headache days used N=85 and analysis of ≥50% responder rate used N=86; for Botox the subgroup Ns used were 396 and 479, respectively.

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

Source: Compiled from Section 2 of the submission.

6.10 As well as the small size of the Study 295 subgroup population, and the questions about adherence to protocol amongst these participants raised by this subgroup

meeting exclusion criteria for the study, there were a number of concerns with the indirect comparisons presented by the submission.

- 6.11 Other than reporting the mean age and proportion of females for the Study 295 subgroup population, the submission did not provide any assessment of potential differences between the subgroup and overall trial populations.
- 6.12 A key outcome used in the indirect comparison (and economic model), proportion of patients with  $\geq 50\%$  reduction in headache days, was not a primary, secondary or exploratory outcome in the erenumab trial. The submission provided no information on how the required data from Study 295 used was collated, in particular whether blinding was maintained. Given that number of headache days is a subjective measure, there was potential for further bias in collection of the required data. The ESC noted that this was a relative rather than absolute outcome, and suggested that an absolute reduction in headache days would be more clinically meaningful.
- 6.13 While the indirect comparison for effectiveness outcomes was based on the subgroup population that corresponded to the proposed PBS population (failed  $\geq 3$  prophylactic medications and naïve to Botox), the data for the safety outcomes were sourced from the overall trial populations. It cannot be assumed that the observed results for the overall trial populations would apply to the subgroup population.

### Comparative effectiveness

- 6.14 The effectiveness results for the comparison of erenumab and Botox were based on the subgroup indirect comparison for two variables, change from baseline in monthly headache days and proportion of patients with  $\geq 50\%$  reduction in mean headache days. Results of these indirect comparisons are provided in the tables below.

**Table 4: Results of the indirect comparison for change from baseline in monthly headache days – erenumab vs. Botox**

Trial	Mean change from baseline (SD) in monthly headache days			WMD (95% CI)
	Erenumab	Placebo	Botox	
Study 295 (12 weeks)	N= [redacted] ( [redacted] )	N= [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)
<b>Indirect mean difference (random effects)</b>				<b>[redacted] (- [redacted], [redacted])</b>

CI=confidence interval; SD=standard deviation; WMD=weighted mean difference; **bold**=statistically significant  
Source: Table 2.29, p56-57 of the submission.

**Table 5: Summary of results of the indirect comparison for proportion of patients with ≥50% reduction in monthly headache days**

Trial	n with event/N (%)		Treatment effect	
	Intervention	Placebo	OR (95% CI)	RR (95% CI)
Erenumab - Study 295 (12 weeks)	■/■ (39.4%)	■/■ (■%)	■ (■, ■)	■ (■, ■)
Botox - Pooled PREEMPT trials (24 weeks)	76/189 (40.2%)	51/207 (24.6%)	2.06 (1.34, 3.16)	1.63 (1.22, 2.19)
<b>Indirect comparison</b>			OR=■ (■, ■)	RR=■ (■, ■)

CI=confidence interval; OR=odds ratio; RR=relative risk  
Source: Table 2.30, p58-59 of the submission.

- 6.15 The indirect comparisons demonstrated a statistically significant difference between erenumab and Botox for mean change in headache days, but no statistically significant difference between erenumab and Botox for proportion of patients with ≥50% reduction in headache days.
- 6.16 The post-hoc subgroup from the erenumab trial including patients who had failed ≥3 prophylactic medications and were naïve to Botox comprised less than ■% of the overall trial population. While the submission argued that the nominated subgroup was applicable to the proposed PBS population as the subgroup had a similar age and proportion of females to that observed in the overall trial, there was no discussion provided by the submission as to whether the subgroup may have differed from the overall trial population on relevant disease characteristics such as duration of chronic migraine, number of headache or migraine days per month.
- 6.17 The data available within the submission for number of migraine days and headache days for the overall trial population and the subgroup is summarised in the table below. Comparisons were conducted during the evaluation to assess the overall trial population and subgroup differences.

**Table 6: Overall trial population and subgroup population baseline values for erenumab**

Outcome	Baseline mean ± SD	
	Overall trial population	Subgroup population
<b>Erenumab</b>	N=190	N=■
Monthly headache days	20.7 ± 3.8	■ ± ■
Monthly migraine days	17.8 ± 4.7	■ ± ■
<b>Placebo</b>	N=286	N=■
Monthly headache days	21.1 ± 3.9	■ ± ■
Monthly migraine days	18.2 ± 4.7	■ ± ■

SD=standard deviation;

Source: Table 2.12, p31 and Table 2.26, p54 of the submission; differences calculated during the evaluation.

- 6.18 There were differences (albeit numerically small) in baseline values between the overall trial population and the subgroup for erenumab, with more migraine and headache days in the subgroup compared to baseline values. For the placebo group, there was essentially no difference between the overall trial population and the subgroup for monthly migraine days, and slightly fewer monthly headache days for the subgroup.

- 6.19 The time point for assessment in Study 295 was 12 weeks and in the Botox trials was 24 weeks. The submission argued that the indirect comparisons were conservative as the treatment effect for erenumab is expected to improve over time, based on the open-label extension study 255. However, as only █% of the patients in Study 255 used the 140 mg/day dose of erenumab and results were sourced from an overall population using the 70mg dose or having changed doses, it is not reasonable to assume that Study 255 results will be representative of longer-term results with the 140 mg/day dose.
- 6.20 Overall, there was a statistically significantly greater reduction in headache days per month for erenumab compared to Botox based on the indirect comparison presented by the submission, and this difference corresponds to that considered clinically meaningful by the PBAC in relation to Botox (2-3 days, p4 July 2013 Botox Public Summary Document). However, there was no statistically significant difference between erenumab and Botox for proportion of patients with a ≥50% reduction in headache days.
- 6.21 The ESC agreed that the issues with the substantial differences in the placebo response rates across the trials and the use of the small subgroup meant that the indirect comparisons (described above) do not support a claim of superiority (see ‘Clinical claim’ below).

### Comparative harms

- 6.22 The table below provides a summary of the results of the indirect comparisons presented by the submission for safety outcomes. As noted above, these comparisons were based on the overall trial populations, and not the nominated subgroup of patients who had failed ≥3 prophylactic medications and for erenumab, were naïve to Botox. As the submission did not provide a comparison of the erenumab subgroup and the overall Study 295 population, it may not be reasonable to assume that overall trial results will apply to the nominated subgroup.

**Table 7: Results of the indirect comparisons between erenumab and Botox for safety outcomes**

Outcome	n with event/N (%)		OR	n with event/N (%)		OR	Indirect OR (95% CI)
	Erenumab	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)	0.2 (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	█/█ (%)	█/█ (%)	█/█ (█, █)	0/687 (0%)	0/692 (0%)	0 (0,0)	█

AE=adverse event; CI=confidence interval; OR=odds ratio; SAE=serious adverse events  
Source: Table 2.31, p60 of the submission.

- 6.23 There were no statistically significant differences between erenumab and Botox for the occurrence of any AE, serious AEs, AEs leading to trial discontinuation or AEs leading to death. It was difficult to draw conclusions regarding the comparative safety of erenumab and Botox given that no information was provided in the submission regarding the specific type of adverse events that were classified as serious AEs, or that may have led to discontinuation. There were data available in the publication of the pooled Botox trials (Dodick 2010) that would have permitted comparison of treatment-related AEs such as injection site pain between erenumab and Botox, however this was not considered by the submission.
- 6.24 A higher proportion of patients in the erenumab group reported treatment-emergent AEs than Botox-treated patients as reported in the pooled analysis of the PREEMPT trials (29.4%; Table 4 of Dodick 2010). The evaluation stated that data for comparable treatment-related AEs across the trials may be informative for assessing the comparative safety. The PSCR presented the indirect comparison with treatment related AEs from Dodick 2010, which demonstrated a statistically significant reduction in favour of erenumab (OR=█████; 95% CI: █████, █████). For injection site pain, the only common treatment related AE in the erenumab and Botox studies, there were no statistically significant differences between erenumab and Botox.
- 6.25 Below is a summary of AEs for erenumab only that was presented in Section 2.5.2 of the submission. The submission did not include between-group comparisons of these AEs, but the information has been presented here to provide a summary of treatment-related events in Study 295.

**Table 8: Treatment-emergent AEs in ≥2% of patients in Study 295 for erenumab**

Adverse event	Erenumab (N=188)	Placebo (N=282)
Any treatment-emergent AE	88 (46.8%)	110 (39.0%)
Injection site pain	7 (3.7%)	3 (1.1%)
Upper respiratory tract infection	6 (3.2%)	4 (1.4%)
Nausea	6 (3.2%)	7 (2.5%)
Nasopharyngitis	3 (1.6%)	16 (5.7%)
Constipation	8 (4.3%)	1 (0.4%)
Muscle spasms	7 (3.7%)	4 (1.4%)
Migraine	5 (2.7%)	3 (1.1%)
Cough	█████ (█████%)	█████ (█████%)
Fatigue	█████ (█████%)	█████ (█████%)
Diarrhoea	█████ (█████%)	█████ (█████%)
Injection site erythema	█████ (█████%)	█████ (█████%)
Rhinitis	█████ (█████%)	█████ (█████%)

Source: Table 2.24, p52 of the submission.

- 6.26 In general, each specific treatment-emergent AE was observed in a small proportion of patients, with each AE for erenumab reported by less than 5% of patients. Injection site pain was the most frequently experienced AE, being reported by just under 4% of patients treated with erenumab. Other common AEs noted in the draft PI are constipation, muscle spasm and pruritus.

6.27 The ESC noted that there was limited longer-term safety evidence available for erenumab, given that the longest trial appears to be the 13 month open-label extension trial Study 295.

### Benefits/harms

6.28 A summary of the comparative benefits of erenumab versus Botox is presented in the table below. As the indirect comparison for safety outcomes did not indicate any statistically significant differences between erenumab and Botox, comparative harms are not presented.

**Table 9: Summary of comparative benefits for erenumab versus Botox**

Benefits								
Indirect comparison: proportion of patients with ≥50% reduction in monthly headache days								
	Eren n/N	PBO n/N	Botox n/N	OR (95% CI)	Event rate/100 patients*			RD (95% CI)
					Eren	PBO	Botox	
Study 295	(█%)	(█%)	-	(█, █)	█	█	-	(█, █)
PREEMPT I and II	-	51/207 (24.6%)	76/189 (40.2%)	2.06 (1.34, 3.16)	-	24.6	40.2	0.16 (0.06, 0.25)
Indirect comparison				OR=█ (█, 10.40)	-			(█, █)
Indirect comparison: change from baseline in monthly headache days								
	Active treatment group			Common arm comparator			Indirect comparison: WMD (95% CI)	
	N	Mean Δ baseline MHD	SD	N	Mean Δ baseline MHD	SD		
Study 295	█	█	█	█	█	█	█ (█, █)	
PREEMPT I and II	231	-7.4	6.6	248	-4.7	6.4		

\* Study 295 had a 12 week double-blind treatment phase and PREEMPT I and PREEMPT II had a 24 week double-blind treatment phase. Eren=erenumab; MHD=monthly headache days; OR=odds ratio; PBO=placebo; RD=risk difference; SD=standard deviation; WMD=weighted mean difference; **bold**=statistically significant  
Source: Table 2.29, p56-57, Table 2.30, p58-59 of the submission.

6.29 Given the ESC’s concerns about the indirect comparison, a statement of benefits/harms has not been presented.

### Clinical claim

6.30 The submission described erenumab as superior in terms of comparative effectiveness and equivalent in terms of comparative safety to Botox. This conclusion is not adequately supported by the evidence presented in the submission.

6.31 There were substantial differences in the placebo response rates and the placebo adverse event rates between the studies.

6.32 The identified subgroup (patients who had failed ≥3 prophylactic medications and were naïve to Botox) comprised less than █% of patients in Study 295. There were only █ patients treated with erenumab, which is a relatively small sample size, particularly in the context of the size of the overall market.

- 6.33 Apart from age and gender, there was no comparison provided of relevant baseline data to assess whether the subgroup differed from either the whole trial population, or whether there were differences between the erenumab and placebo arms of Study 295 for the subgroup. Analyses conducted during the evaluation revealed a difference between the overall trial population and the subgroup in Study 295 for monthly migraine days.
- 6.34 As acknowledged by the submission, headache days are a subjective outcome. In addition, the change from baseline in headache days per month was not a primary or secondary outcome in Study 295 but was an exploratory outcome, and the proportion of patients with a  $\geq 50\%$  reduction in headache days was not an outcome, either primary, secondary or exploratory, in Study 295.
- 6.35 While the indirect comparison for effectiveness outcomes was based on the subgroup population that corresponded to the proposed PBS population (failed  $\geq 3$  prophylactic medications and naïve to Botox) the data for the safety outcomes was sourced from the overall trial populations. It cannot be assumed that the observed results for the overall trial populations will apply to the PBS-population relevant subgroup.
- 6.36 It is difficult to draw conclusions regarding the comparative safety of erenumab and Botox given that no information has been provided by the submission regarding the specific type of adverse events that were classified as serious AEs, or that may have led to discontinuation.
- 6.37 The ESC noted that the evaluation suggested, given the substantive points made above regarding the indirect comparison, that a more reasonable therapeutic conclusion may be that erenumab and Botox are non-inferior in regard to both effectiveness and safety. However, given the limitations of the data (small subgroup with high risk of bias), the ESC was not confident that the data adequately supported a claim of non-inferiority.
- 6.38 A recent review of CGRP inhibitors (erenumab, eptinezumab, fremanezumab, galcanezumab) stated that the efficacy of all four drugs is modest over placebo and overall is comparable with oral preventative treatments (Paemeleire 2018).

### ***Economic analysis***

- 6.39 The submission presented a cost-utility analysis based on an indirect comparison of the erenumab randomised trial Study 295 and the pooled results of the two Botox randomised trials, PREEMPT I and PREEMPT II. The submission presented comparisons against Botox and best supportive care (BSC). As the indirect comparisons presented by the submission did not support a claim of superiority for erenumab over Botox, a cost utility analysis was not supported and likely invalid.
- 6.40 The ESC considered that the comparison with BSC was not informative for assessing the cost-effectiveness of erenumab. This view was based on the clinical place of

erenumab which is unlikely to be “last in line”, as well as concerns about the subgroup (and small sample size) from the erenumab trial and the model structure and assumptions relating to the Botox comparison.

6.41 The table below provides a summary of the key components of the economic evaluation.

**Table 10: Summary of model structure and rationale**

<b>Component</b>	<b>Summary</b>
Time horizon	5 years in the model base case vs. 12 weeks in the erenumab trial and 24 weeks in the Botox trials.
Outcomes	Quality-adjusted life years (QALYs).
Methods used to generate results	Markov cohort analysis.
Health states	6 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. While this corresponded to the length of the erenumab trial (12 weeks), it did not correspond to the requested restriction, where assessment for continuing therapy occurs at 24 weeks (6 months).
Transition probabilities	Study 295 and the indirect comparison versus Botox.

Source: Table 3.1, p66 of the submission.

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

**Table 11: Key drivers of the model**

Description	Method/Value	Impact
Clinical efficacy	<ul style="list-style-type: none"> <li>The economic model was based on results from the indirect comparison of erenumab and Botox for proportion of patients with ≥50% reduction in headache days. There was no statistically significant difference between erenumab and Botox for this outcome.</li> <li>The model used an assessment point of 24 weeks to determine responders. While this was consistent with the requested restriction and the Botox data, the erenumab trial used a 12 week assessment point.</li> <li>For rates of discontinuation the model used data from the overall trial populations, which was not consistent with the model population or the proposed PBS population.</li> </ul>	High, favours erenumab
Parametric distributions	<ul style="list-style-type: none"> <li>The 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 determination of MMD distributions was done using parametric models based on Study 295 data. MMDs including data from the 70 mg/day dose of erenumab were used in the assessment of response period while MMDs based on the overall trial population were used for the remainder of the model (with patients returning to baseline MMD distributions if they discontinued). As such, the populations used to determine the MMD distributions did not match the model or proposed PBS population.</li> </ul>	Moderate, favours erenumab
Extrapolation	<ul style="list-style-type: none"> <li>The submission stated that extrapolation of the clinical data was in principle performed on the last observation carried forward (LOCF) basis – patients who were deemed as responders at 12 weeks continue on treatment and remain in response into the post-assessment phase, although they were subject to the risk of treatment discontinuation and death. As such, for patients who do not die due to all-cause mortality or do not discontinue due to AEs or other reasons, the model assumed that the response over 12 weeks in Study 295 was maintained up to 5 years. Given the lack of long-term data for erenumab, it is not likely to be reasonable to assume that response may be maintained over such a time period.</li> </ul>	High, favours erenumab

Source: compiled from Section 3 of the submission during the evaluation.

6.43 The results of the economic evaluation are provided below, for the comparisons against both Botox and BSC.

**Table 12: Results of the economic evaluation**

<b>Erenumab vs. Botox with corrected odds ratio (■■■■)a</b>	<b>Erenumab</b>	<b>Botox</b>	<b>Increment</b>
Costs	\$■■■■	\$■■■■	\$■■■■
QALYs	■■■■	■■■■	■■■■
<b>Incremental cost/extra QALY gained</b>			\$■■■■
<b>Erenumab vs. BSC</b>	<b>Erenumab</b>	<b>BSC</b>	
Costs	\$■■■■	\$■■■■	\$■■■■
QALYs	■■■■	■■■■	■■■■
<b>Incremental cost/extra QALY gained</b>			\$■■■■

BSC=best supportive care

a Analysis vs Botox has been updated by replacing the incorrect odds ratio with the correct odds ratio as acknowledged in the PSCR (p5) Source: Table 3.32, p108 of the submission and the Excel workbook 'Attachment 7\_Section 3 Erenumab'.

6.44 The base case ICER versus Botox is not likely to accurately represent the cost-effectiveness of erenumab.

- 6.45 The efficacy outcome applied in the economic model (50% responder rate based on the indirect comparison of erenumab and Botox) is not valid and did not reach statistical significance.
- 6.46 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.
- 6.47 The rates of discontinuation used in the model 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 specific to the model provided in the submission.
- 6.48 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 et al, 2012<sup>5</sup>.
- 6.49 The model assumed that the availability of erenumab would lead to fewer specialist visits, due to its relatively simple administration, and factored this in as a cost offset to the MBS. The ESC advised that self-administration was more likely to lead to wastage compared with specialist administration, and that the potential financial (as well as effectiveness) impact of this was worth consideration.
- 6.50 A lesser issue is that maintenance healthcare costs were based on data from a European study which is likely to differ to the Australian context. Sanderson et al., 2013<sup>6</sup>, observed differences between Australia and other countries in service utilisation due to chronic migraine. The ESC noted that this may have led to bias in the estimates of the disease management costs, but that these costs do not impact the ICER substantially.
- 6.51 The economic model determined health state costs and utility values using MMD distributions. There were a number of issues with the MMD distributions:
- The trial used monthly headache days (MHDs), so MMDs were calculated using parametric techniques, and the submission did not present the full model fit criteria, only Akaike's information criterion.
  - Baseline distributions included data for the 70 mg dose of erenumab; the submission claimed this would have no impact; however this claim was not supported.
  - The economic model applied an assessment point of 24 weeks for responders for consistency with the requested PBS restriction and Botox listing. However, the

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<sup>5</sup> Stafford et al (2012). EQ-5D™-derived utility values for different levels of migraine severity from a UK sample of Migraineurs. *Health and Quality of Life Outcomes* 2012, 10:65

<sup>6</sup> Sanderson, J C, et al (2013). Headache-related health resource utilisation in chronic and episodic migraine across six countries. *Journal of Neurology, Neurosurgery & Psychiatry* 2013, 84. 1309–1317

MMD distributions applied in the economic model appeared to define responders and non-responders at 12 weeks, which was the assessment point in the erenumab clinical trial.

- The use of a sample in which over 80% of patients are not eligible for the proposed PBS listing to determine MMD distributions raised questions regarding the applicability of the derived values.
- Lastly, the ESC questioned the ‘tail’ of the distribution, as it showed some responders with as many as 28 MMDs (implausible due to the definition of the outcome), and the fact that 36% of responders were shown to be reduced to just one MMD.

- 6.52 While the same MMD distributions were applied to the erenumab and Botox arms of the model, limiting their impact on the ICER, the use of varying sources for model variables that do not correspond to the proposed PBS population, along with application of identical values to the two treatment arms means that the ability of the model to accurately represent the cost-effectiveness of erenumab is limited. The economic model was therefore essentially running on the treatment effect (proportion of patients with  $\geq 50\%$  reduction in monthly headache days). This treatment effect was not statistically significantly different between erenumab and Botox, and the base case ICER at just less than \$45,000/QALY - \$75,000/QALY appears to be a function of a number of assumptions that may not reflect use in clinical practice.
- 6.53 The utilities had little impact on the model, as the same values were applied to both arms. 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)<sup>7</sup>. The ESC noted that utility differences in Brown et al (2008) were smaller than those presented in the submission.
- 6.54 The model demonstrated sensitivity to differential response rates and to the time horizon. Benefits appeared to increase considerably once a year passed. Given that there is no long-term evidence for maintenance of response for erenumab, the ICERs based on shorter time periods (6 months: \$105,000/QALY - \$200,000/QALY and 1 year: \$75,000/QALY - \$105,000/QALY) may better represent the cost-effectiveness of erenumab versus Botox given the lack of longer-term data. Except to state that extrapolation is important, the submission did not consider extrapolation of the observed short-term (12 weeks or 3 months) benefit and assumed that the benefit would be maintained on a last observation carried forward basis.

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<sup>7</sup> 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

6.55 Given the above limitations, it is not likely that the base case versus either Botox or BSC accurately estimates the cost-effectiveness of erenumab.

**Drug cost/patient/year: \$ [REDACTED]**

6.56 The table below provides a summary of annual treatment costs for erenumab. The submission provided an estimate of costs without the proposed stopping rule (50% responder rate) which assumed 13 doses of erenumab over a year (\$ [REDACTED] per dose) resulting in an annual cost of \$ [REDACTED]. Estimation of annual cost with the stopping rule applied ([REDACTED]% of erenumab-treated patients were responders), resulted in an average annual cost of \$ [REDACTED].

**Table 13: Annual treatment costs per patient for erenumab**

	Erenumab
<b>Annual cost with no stopping rule</b>	
Drug cost per dose	\$ [REDACTED]
Administration cost	-
Total drug cost	\$ [REDACTED]
Number of treatment cycles	13
<b>Total cost over 12 months</b>	<b>\$ [REDACTED]</b>
<b>Average annual cost with stopping rule in place</b>	
Number of treatment cycles to response assessment (24 weeks)	6
Response rate <sup>a</sup>	[REDACTED]%
Number of treatment cycles post-assessment to 12 months	7
<b>Cost over 12 months for responders</b>	<b>\$ [REDACTED]<sup>b</sup></b>

<sup>a</sup> The response rate for erenumab is sourced from the indirect comparison, see Section 2.6 of the commentary.

<sup>b</sup> \$ [REDACTED] = (\$ [REDACTED] × 6) + ([REDACTED]% × 7 × \$ [REDACTED])

Source: Table 3.30, p107 of the submission

6.57 The annual cost with the stopping rule (proportion of patients with ≥50% reduction in headache days per month) was based on the results of the indirect comparison. Given that this indirect comparison had a number of potential sources of bias (detailed above), the proportion responding may not represent what will occur in clinical practice.

**Estimated PBS usage & financial implications**

6.58 This submission was considered by DUSC. The submission applied data from the June 2017 DUSC review of Botox (Botulinum toxin type A for chronic migraine: 24-month predicted versus actual analysis) along with PBS statistics for the use of Botox and uptake assumptions to estimate usage and financial implications of the PBS listing of erenumab. The table below provides a summary.

**Table 14: Estimated use and financial implications**

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

<sup>a</sup> Assuming 13.04 scripts per year as estimated by the submission. The submission also applied a half-year correction for patients in their first year of treatment (6.52 scripts).

<sup>b</sup> The submission's Excel Workbook ('Attachment 8\_Utilisation-and-financial\_estimates') in the worksheet 'Net changes – MBS' applied the cost for Botox administration (\$106.15) instead of the cost for specialist consults (\$64.20). This was corrected during the evaluation, with resultant changes made to the overall net cost to Government.

Source: Table 14, 5.05.COM.20

- 6.59 Based on the estimated usage of erenumab and substitution for Botox, along with a decrease in MBS costs due to displaced Botox administration, the overall estimated net cost to the Government for the first 6 years of erenumab listing was more than \$100 million. At year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be \$30 - \$60 million.
- 6.60 There is potential this could be an underestimate given the relatively small uptake in Year 1 (30% of eligible patients), the lack of inclusion of MBS costs for patients visiting a specialist to initiate erenumab, as well as the use of the known Botox patient pool to estimate the eligible treatment population, which was not likely to identify all eligible chronic migraine patients. DUSC considered that patients for whom Botox was unacceptable or inconvenient may take up erenumab due to the relative ease of administration and/or potential for continuation by a GP. DUSC also questioned, given the range of presentations of migraine, whether the population treated with Botox is the same as the population who would be treated with erenumab.
- 6.61 The submission extrapolated the available Botox data to estimate the total number of patients in 2018 and the first 6 years of the proposed listing (2019 to 2024). An adjustment was made to the linear growth rate to reflect what the submission described as a more reasonable market curve. No justification for the market growth rates was provided. DUSC considered that the extrapolation of the Botox market out to 2024 was highly uncertain because it was based on a limited number of data points.

- 6.62 DUSC advised that there is a risk that erenumab could be used outside of its requested restriction in patients who are not naïve to Botox, and noted that the erenumab trial included patients previously treated with Botox (23%). DUSC considered it unreasonable to exclude patients where there is evidence of a clinical benefit.
- 6.63 The submission applied the Botox continuation rate to erenumab. The submission considered that there was a medium degree of uncertainty regarding Botox continuation rates, as only 24 months of follow-up were available at the time of the DUSC analysis. DUSC considered that the continuation rate from the erenumab trial should be used in the base case financial estimates, as this is the source of the efficacy data, and as the cost-effectiveness of prolonged Botox use has not been established. The sponsor agreed with this proposed approach in its Pre-PBAC Response.
- 6.64 As discussed in Section 2 above:
- A higher proportion of neurologists might prescribe erenumab compared with Botox, which may drive higher uptake than anticipated;
  - there is a risk of continuation beyond the trial duration, for example, a risk of indefinite continuation if response is not adequately assessed by GPs. The cost-effectiveness of erenumab in this scenario is unknown.
- 6.65 The number of erenumab prescriptions was calculated based on full compliance (13.04 prescriptions per year), and the submission base case assumed a one-for-one patient exchange of erenumab for Botox at full compliance; DUSC advised that full compliance with Botox or erenumab was unlikely, and considered that this may overestimate cost-offsets. Patients in the 'growth population' who have not previously received Botox may not have the same extent of neurologist consultations and therefore fewer or no offsets. They also should have no offsets applied for Botox administration or Botox supply. DUSC also considered it is possible more patients would be referred to neurologists with a new treatment available, so the offsets for neurologist consultations may not be realised.
- 6.66 DUSC noted that the sponsor is also seeking TGA registration for use in episodic migraine, which could be a very large market. Clinicians might commence patients with episodic migraine on erenumab under the chronic migraine listing, particularly given the TGA delegate's overview identifies evidence of clinical benefit in episodic migraine.
- 6.67 The submission provided, in a sensitivity analysis, estimated costs associated with use of erenumab by patients who were not captured in the base case eligible patient pool; i.e. patients who have not been supplied Botox and therefore were not captured in the DUSC review. However, the submission considered it highly uncertain whether this group of patients exists. The additional patients estimated by

the submission would add an estimated \$10 - \$20 million over the first 6 years of listing to the more than \$100 million already estimated in the base case. These additional costs were likely to be underestimated, given the submission assumed the eligible patient pool would only increase by 10% (over the existing Botox patient pool), and the uptake rate was half of what was used for the base case estimates. If the additional proportion of patients not treated with Botox were increased from 10% to 25%, estimated net costs to the PBS over the first 6 years of listing would increase to \$30 - \$60 million. If uptake rates matching those used for the base case estimates were also applied, the estimated additional cost over the first 6 years of listing would be \$60 - \$100 million.

- 6.68 Overall, DUSC considered the estimates presented by the submission of the number of patients treated with erenumab and associated costs were underestimated. Given it is highly likely there would be eligible patients in addition to those captured in the DUSC review (e.g. patients who preferred not to use Botox with its injection schedule; patients in small centres or rural areas who could not access a neurologist to administer Botox), it may have been more appropriate to include these additional patients as part of the base case estimates. Inclusion of this additional \$60 - \$100 million would increase the estimated net cost to the Government over the first 6 years of listing to more than \$100 million from the more than \$100 million estimated in the submission's base case.

### **Quality Use of Medicines**

- 6.69 The submission did not provide discussion of quality use of medicines. DUSC was concerned about this, particularly given that erenumab is a first in class medicine with limited safety data available.
- 6.70 DUSC noted the available safety data is largely for the 70 mg dose, which was approved by the US FDA, while the proposed PBS listing is being sought for the 140 mg dose.
- 6.71 DUSC considered a quality use of medicines strategy for erenumab should also consider GP training for continuing and discontinuing therapy, and recognition of medication overuse headache.

### **Financial Management – Risk Sharing Arrangements**

- 6.72 The submission stated that if the PBAC were to recommend erenumab for chronic migraine the sponsor would be willing to share the risk caused by the uncertainty in the estimates and to negotiate expenditure caps applicable specifically to erenumab. The submission made the following points regarding the proposed risk-sharing arrangement:
- The arrangement may include allowance for the uncertain impact of any patients not treated with Botox under the existing treatment algorithm.

- It should not include risk to Commonwealth expenditure identified in the June 2017 DUSC review of the potential use of Botox beyond the restriction for its cosmetic benefits.
- Any negotiated caps should also take known treatment patterns identified in the June 2017 DUSC review into account, and should not be linked to estimates made by the sponsor at the time of the Botox submission.

6.73 There was no further information provided on the potential risk-sharing arrangement.

*For more detail on 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 that the submission had neither adequately justified the place in therapy nor justified the proposed PBS population that may exclude migraine patients who may benefit from this treatment. The subgroup analysis used as a basis of the clinical claim that erenumab was superior to Botox had significant limitations resulting in a cost-effectiveness estimate that was highly unreliable for decision making.
- 7.2 The PBAC acknowledged the clinical need for effective prophylactic treatment of chronic migraine, and the significant number of consumer comments received in regard to this submission. The Committee noted that the comments highlighted the inefficacy and limitations of botulinum toxin (Botox), the submission's nominated comparator, and the difficulties associated with its administration. The comments reflected the significant impact that migraines have on physical, mental, and social wellbeing and the opportunity that erenumab presents. The PBAC noted that comments reflected the community's interest in treatments being available for patients with chronic migraine (the subject of this submission) and episodic migraine (a population included in the TGA's registration of erenumab). The PBAC noted the significant burden of disease of migraines, with more than a tenth of the Australian population estimated to be affected by migraine.
- 7.3 The Committee noted that the submission was made under the TGA/PBAC parallel process and the proposed dose of erenumab in the submission was 140 mg. The PBAC noted that erenumab was registered on the ARTG immediately before the PBAC meeting. The latest version of the production information provided to the Committee with the Pre-PBAC response, which stated '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 PBAC noted that this was in line with the initial dose recommended by the US Food and Drugs Administration. As the submission had only proposed a dose of 140 mg and as the clinical trial outcomes suggested that there was little or no difference

between a treatment dose of 140 mg and 70 mg, the PBAC considered that the impact of the majority of patients being treated with 70mg on the submission is unknown.

- 7.4 The submission placed erenumab as a later-line therapy in Botox naïve patients following failure of at least three prophylactic agents. The PBAC considered that the clinical place in therapy of erenumab is unclear, but considered that there was no demonstration that prior treatment for chronic migraine modifies treatment effect. As such, the PBAC considered that there was no justification for excluding patients who had previously been treated with Botox, as this patient population may benefit from treatment as shown in clinical trials, but agreed that concomitant use of erenumab and Botox should not be permitted.
- 7.5 Given the evidence that shows erenumab provides benefit to patients with episodic migraine (trial ARISE/ NCT02483585 and STRIVE/NCT02456740), as well as chronic migraine, the Committee agreed with its DUSC's advice that it is very likely erenumab would be used outside of the proposed PBS population (chronic migraine only). The PBAC noted that erenumab is the first CGRP inhibitor seeking PBS listing, with a range of new targeted therapies entering the market. The PBAC considered that the clinical place of erenumab may become clearer with further experience in using these medicines.
- 7.6 The PBAC noted that the restriction proposed in the submission was based on the current Botox listing, as the submission claimed that erenumab would be used in the same clinical place as Botox. As the Committee did not agree with the submission's clinical place, the PBAC acknowledged that there will be difference in the listing compared to Botox, depending on the agreed clinical place of erenumab.
- 7.7 The PBAC supported a listing with an initial prescription, initiated by neurologists or FRACP/FFPMANCA-accredited pain/headache specialists, and a continuing prescription for patients achieving a response with initial treatment. The PBAC considered that the time of response assessment did not necessarily need to match Botox (24 weeks), but should be informed by the product information and clinical guidelines. While the PBAC noted that prescribing of continuing therapy by a GP would increase patient access to treatment, the Committee shared the DUSC's concerns that the proposed restriction does not require a specialist to assess the response to erenumab at any point after initiation. The PBAC considered that a specialist should be involved in the continuing ongoing treatment with erenumab, and that this should be addressed in a resubmission.
- 7.8 The PBAC considered that Botox was an appropriate comparator if the clinical place for erenumab is limited to later line therapy as a substitute for Botox. However, with the PBAC's view of the clinical place of erenumab, and noting that there is likely a population who will not be treated with Botox due to the inaccessibility of neurologists or the discomfort associated with the administration, Botox may not be

the appropriate comparator. The PBAC considered that agreeing the clinical place of erenumab will inform the comparator choice.

- 7.9 The PBAC noted that the efficacy and safety of erenumab was predominately based Study 295, a phase 2, randomized, double-blind, placebo-controlled trial. The PBAC noted that in the whole trial population, erenumab reported a statistically significant reduction in monthly headache days (MHD) compared to placebo [-2.46, (95% CI: -3.52, -1.41),  $p < 0.001$ ]. While a relatively modest treatment effect after 12 weeks of treatment in patients with a baseline of approximately 20 MHD, the PBAC recalled that in considering Botox for chronic migraine in July 2012, it was accepted that a change of two to three headache days per month as shown in the Botox PREEMPT trials (24 weeks) represented a clinically meaningful outcome.
- 7.10 The PBAC noted that the clinical claim of the submission was based on an indirect comparison of a sub-group analysis with patients who had failed  $\geq 3$  prophylactic medications and were naïve to Botox. The PBAC shared the ESC's concern about the indirect comparison in the submission. The PBAC noted the significant differences between the response rates in the placebo arms of the erenumab and Botox clinical trials. The PBAC also noted the sponsor's claim in its Pre-PBAC Response that the different response rates were adjusted for in the odds ratios used to present the results of the trials. The assumption of transitivity inherent in the indirect comparison is contingent on consistent response rates to the common treatment (placebo), so the Committee advised that this discrepancy was likely to invalidate the clinical claim that erenumab is superior compared to Botox.
- 7.11 Further, the PBAC noted that only [REDACTED] of the [REDACTED] patients in the open-label extension trial on which the clinical claim and economic model are based were treated with erenumab. The PBAC considered this sub-group insufficient, given that the population eligible for treatment in Australia was estimated to be 300,000 – 700,000 people. Basing the analysis on this subgroup became necessary because the majority of patients in the whole trial ([REDACTED]/476) did not match the proposed PBS population, as failure of  $\geq 3$  prophylactic migraine medications was an exclusion criterion for the whole trial, but an inclusion criterion for the proposed PBS listing. However, the definition of failure for the whole trial referred only to insufficient efficacy, whereas the definition for the sub-group included both efficacy and tolerability issues. Thus, 86 patients who had failed  $\geq 3$  prophylactic migraine medications were included in the trial nonetheless.
- 7.12 The PBAC did not accept the submission's claim that erenumab as superior in terms of comparative effectiveness and equivalent in terms of comparative safety to Botox, given the Committee's concerns about the clinical evidence to support the indirect comparison. The PBAC considered that the Study 295 did support a claim of superior efficacy of erenumab over placebo. The PBAC further noted that erenumab was easier to administer compared to Botox, and that many consumer comments highlighted the negative aspects of Botox treatment.

- 7.13 Based on the limitations of the clinical evidence provided, the PBAC agreed with the ESC that use a cost-utility analysis to assess the cost-effectiveness of erenumab over Botox was unreliable.
- 7.14 The PBAC also questioned the assumption that for patients who did not discontinue or die due to all-cause mortality, the response over 12 weeks would be maintained for up to 5 years. Given the lack of long-term data for erenumab, it is not likely to be reasonable to assume that response would be maintained over such a time period.
- 7.15 The PBAC considered the derivation of the distribution of monthly migraine days and the resulting utility estimates sub-optimal. The derivation of monthly migraine days using parametric techniques was necessary, because the outcome used in the trial was monthly headache days not monthly migraine days. However, the majority (■■■%) of the population on which the estimation was based did not fit the criteria for the proposed PBS population. In addition, headache severity was not factored into the utility estimates, despite evidence that it has significant influence on the overall wellbeing of patients who experience migraines.
- 7.16 The PBAC noted the estimates of the number of people with chronic migraine in Australia, which varied between 300,000 and 700,000 depending on the assumptions used. The PBAC advised that this ambiguity surrounding the prevalence of chronic migraine introduced significant uncertainty into the estimates of the financial implication of listing erenumab on the PBS.
- 7.17 The PBAC agreed with its DUSC that the extrapolation of available Botox data to estimate the total number of patients in 2018 and the first 6 years of the proposed listing (2019 to 2024) was highly uncertain because it was based on a limited number of data points.
- 7.18 The PBAC noted DUSC advice that the continuation rates applied in the submission were likely to be underestimates.
- 7.19 The PBAC agreed with DUSC that the utilisation of erenumab and resulting financial impact were likely to have been significantly underestimated in the submission. In particular, given that erenumab has been shown to be beneficial for patients with episodic migraine, PBAC noted the risk of leakage to a much broader population. Further, the PBAC noted that the impact of increasing prescribers (for example, pain/headache specialists) who can initiate treatment had not been factored in the utilisation estimates.
- 7.20 The PBAC re-iterated that erenumab has been shown to provide a clinical benefit to a large population of Australian with a need for new treatment options. The PBAC considered that any resubmission should be a major submission, and should:
- re-evaluate and justify the clinical place of erenumab and the comparator(s), and how this aligns with the whole clinical trial population and with the final product information with regards to the 70 mg and 140mg doses;

- address the concerns raised by the PBAC, ESC and DUSC;
- based on the clinical evidence and the uncertainty in assumptions in the economic model, 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; and
- propose a risk sharing arrangement including caps on Government expenditure, preferably for the treatment of all migraine.

7.21 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**

Novartis remains committed to working with the PBAC to enable reimbursed access to erenumab for Australian patients with migraine.