

5.06 FREMANEZUMAB, Injection 225 mg in 1.5 mL pre-filled syringe, Ajovy[®], Teva Pharma Australia Pty Ltd

1 Purpose of application

- 1.1 The submission requested an Authority Required (Streamlined) listing of fremanezumab (225 mg monthly or 675 mg every 3 months) for the treatment of patients with chronic migraine who have had an inadequate response, intolerance or a contraindication to ≥ 3 prophylactic migraine medications (referred to herein as ‘patients with ≥ 3 prior treatment failures’). The PBAC has not previously considered fremanezumab for the treatment of chronic migraine.
- 1.2 The listing was requested on the basis of a cost-minimisation analysis (CMA) compared to botulinum toxin type A (referred to herein as Botox[®]), and a cost-effectiveness analysis compared to best supportive care (BSC).

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

Component	Description
Population	Patients with chronic migraine who have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications, including: <ul style="list-style-type: none"> - Patients who are eligible to be treated with Botox but are either unwilling due to a needle or Botox phobia, or who are unable to access treatment from a Botox-accredited neurologist (“Botox ruled out” subpopulation). - Patients who are eligible and willing to be treated with Botox (“Botox eligible” subpopulation). - Patients who have tried and failed or are intolerant to Botox (“Botox failed” subpopulation).
Intervention	Fremanezumab 225 mg subcutaneously every 4 weeks or fremanezumab 675 mg subcutaneously every 12 weeks.
Comparator	Primary: Botox administered by intramuscular injection every 12 weeks to 31-39 sites; best supportive care. Supportive: erenumab 70 mg or 140 mg subcutaneously every 4 weeks; galcanezumab 120 mg subcutaneously once a month (following initial 240 mg loading dose).
Outcomes	Reduction in monthly migraine days; reduction in monthly headache days; proportion of patients achieving a response ($\geq 50\%$ reduction from baseline in monthly migraine days).
Clinical claim	In patients with chronic migraine and with ≥ 3 prior treatment failures: <ul style="list-style-type: none"> - Fremanezumab is superior in terms of effectiveness and non-inferior in terms of safety compared to best supportive care (placebo). - Fremanezumab is non-inferior in terms of effectiveness and safety compared to Botox, erenumab and galcanezumab.

Source: Table 1.1, p.2 of the submission.

2 Requested listing

- 2.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
FREMANEZUMAB 225 mg in 1.5mL solution for injection, 150 mg/1mL x 1 pre-filled pen	1	1	2	Published: \$ [REDACTED] Effective: \$ [REDACTED]	Ajovy®, TEVA

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	N/A Chronic
Severity:	N/A -
Condition	Migraine
PBS Indication:	Chronic migraine
Treatment phase:	Initial <i>treatment (monthly dosing)</i>
Restriction: 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
Treatment criteria:	Must be treated by a specialist neurologist, or a pain specialist <i>pain medicine physician accredited or experienced in treating headache</i>

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<p>Clinical criteria:</p>	<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 fremanezumab <i>this medicine</i></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 fremanezumab <i>this medicine</i></p> <p>OR</p> <p>Patient must have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications and subsequently experienced an inadequate response, intolerance or a contraindication (which may include needle or toxin phobia) to botulinum toxin type A for chronic migraine prior to commencement of treatment with fremanezumab</p> <p>AND</p> <p><i>Patient must be appropriately managed for medication overuse headache, prior to initiation of treatment with this medicine</i></p> <p>AND</p> <p><i>The treatment must not be in combination with PBS-subsidised botulinum toxin type A or a PBS-subsidised anti-calcitonin gene-related peptide (anti-CGRP) drug for chronic migraine</i></p> <p>AND</p> <p><i>The treatment must be administered on a monthly dosing schedule</i></p>
<p>Population criteria:</p>	<p>Patient must be aged 18 years or older</p> <p>A maximum of 1 initiation cycle of 3 injections will be authorised under this restriction in a lifetime. Patients who have previously responded to this medication and have in the past met the continuation criteria may recommence treatment under the continuation criteria and do not require re-initiation.</p>
<p>Prescriber instructions:</p>	<p>Prophylactic migraine medications such as are propranolol, amitriptyline, methysergide, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate cyproheptadine or topiramate</p> <p><i>A baseline measurement of the number of migraine days per month must be documented in the patient's medical records.</i></p> <p>-A maximum of 1 initiation cycle of 3 injections will be authorised under this restriction in a lifetime. Patients who have previously responded to this medication and have in the past met the continuation criteria may recommence treatment under the continuation criteria and do not require re-initiation.</p>
<p>Administrative Advice</p>	<p>This drug is not PBS-subsidised for use in combination with botulinum toxin type A for chronic migraine or another anti-CGRP for chronic migraine.</p> <p><i>No increase in the maximum quantity or number of units may be authorised</i></p> <p><i>No increase in the maximum number of repeats may be authorised.</i></p>

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Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
FREMANEZUMAB 225 mg in 1.5mL solution for injection, 150 mg/1mL x 1 pre-filled pen	1	1	5	Published: \$ [REDACTED] Effective: \$ [REDACTED]	Ajovy®, TEVA

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	N/AChronic
Severity:	N/A -
Condition	Migraine
PBS Indication:	Chronic migraine
Treatment phase:	First continuation treatment (monthly dosing)
Restriction:	<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
Treatment criteria:	<p>Must be treated by a neurologist or a pain specialist for achieving the continuation criterion of achieving and maintaining a 50% or greater reduction from baseline in the number of migraine days per month after 3 months in order to be eligible for continuing PBS-subsidised treatment. After this assessment future scripts can be written by general practitioners</p> <p>Must be treated by a specialist neurologist, or a specialist pain medicine physician accredited or experienced in treating headache</p>
Clinical criteria:	<p>Patient must have previously received PBS-subsidised initial treatment with this drug for this condition</p> <p>AND</p> <p>Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine days per month in order to be eligible for continuing PBS-subsidised treatment</p> <p>AND</p> <p>The treatment must not be in combination with PBS-subsidised botulinum toxin type A or a PBS-subsidised anti-calcitonin gene-related peptide (anti-CGRP) drug for chronic migraine</p> <p>AND</p> <p>The treatment must be administered on a monthly dosing schedule</p> <p>AND</p> <p>Patient must continue to be appropriately managed by his or her practitioner for medication overuse headache, prior to initiation of treatment with fremanezumab</p>

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Population criteria:	Patient must be aged 18 years or older Patients who have previously responded to this medication and have in the past met the continuation criteria may recommence treatment under the continuation criteria and do not require re-initiation.
Prescriber instructions:	Prophylactic migraine medications such as propranolol, amitriptyline, methysergide, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate cyproheptadine or topiramate. Patients who have previously responded to this medication and have in the past met the continuation criteria may recommence treatment under the continuation criteria and do not require re-initiation.
Administrative Advice	This drug is not PBS subsidised for use in combination with botulinum toxin type A for chronic migraine or another anti-CGRP for chronic migraine. <i>No increase in the maximum quantity or number of units may be authorised</i> <i>No increase in the maximum number of repeats may be authorised.</i>

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
FREMANEZUMAB 225 mg in 1.5mL solution for injection, 150 mg/1mL x 1 pre-filled pen	1	1	5	Published: \$ [REDACTED] Effective: \$ [REDACTED]	Ajovy®, TEVA

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	<i>Chronic</i>
Severity:	-
Condition	<i>Migraine</i>
PBS Indication:	<i>Chronic migraine</i>
Treatment phase:	<i>Subsequent continuing treatment (monthly dosing)</i>
Restriction:	<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
Treatment criteria:	<i>Must be treated by, or in consultation with a specialist neurologist; or Must be treated by, or in consultation with a specialist pain medicine physician accredited or experienced in treating headache</i>

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Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition under the First continuing treatment restriction AND Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine days per month in order to be eligible for continuing PBS-subsidised treatment; AND The treatment must not be in combination with PBS-subsidised botulinum toxin type A or a PBS-subsidised anti-calcitonin gene-related peptide (anti-CGRP) drug for chronic migraine AND The treatment must be administered on a monthly dosing schedule AND Patient must continue to be appropriately managed for medication overuse headache</p>
Population criteria:	Patient must be aged 18 years or older
Prescriber instructions:	-
Administrative Advice	<p>No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised.</p>

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
FREMANEZUMAB 225 mg in 1.5mL solution for injection, 150 mg/1mL x 1 pre-filled pen	3	3	0	Published: \$ [REDACTED] Effective: \$ [REDACTED]	Ajovy®, TEVA

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	Chronic
Severity:	-
Condition	Migraine
PBS Indication:	Chronic migraine
Treatment phase:	Initial treatment (3 monthly dosing)
Restriction:	<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
Treatment criteria:	Must be treated by a specialist neurologist or a pain specialist pain medicine physician accredited or experienced in treating headache

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Clinical criteria:	<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 <i>this medicine</i></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 <i>this medicine</i></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 <i>this medicine</i></p> <p>AND</p> <p>The treatment must not be in combination with PBS-subsidised botulinum toxin type A or a PBS-subsidised anti-calcitonin gene-related peptide (anti-CGRP) drug for chronic migraine</p> <p>AND</p> <p>The treatment must be administered on a 3 monthly dosing schedule</p>
Population criteria:	Patient must be aged 18 years or older
Prescriber instructions:	<p>Prophylactic migraine medications such as are propranolol, amitriptyline, methysergide, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate, cyproheptadine or topiramate.</p> <p>A baseline measurement of the number of migraine days per month must be documented in the patient's medical records</p>
Administrative Advice	<p>No increase in the maximum quantity or number of units may be authorised</p> <p>No increase in the maximum number of repeats may be authorised.</p>

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
FREMANEZUMAB 225 mg in 1.5mL solution for injection, 150 mg/1mL x 1 pre-filled pen	3	3	1	Published: \$ [REDACTED] Effective: \$ [REDACTED]	Ajovy®, TEVA

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	Chronic
Severity:	-
Condition	Migraine
PBS Indication:	Chronic migraine
Treatment phase:	First continuing treatment (3 monthly dosing)
Restriction:	<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

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Treatment criteria:	<i>Must be treated by a specialist neurologist or a specialist pain medicine physician accredited or experienced in treating headache</i>
Clinical criteria:	<i>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 in order to be eligible for continuing PBS-subsidised treatment AND The treatment must not be in combination with PBS-subsidised botulinum toxin type A or a PBS-subsidised anti-calcitonin gene-related peptide (anti-CGRP) drug for chronic migraine AND The treatment must be administered on a 3 monthly dosing schedule AND Patient must continue to be appropriately managed for medication overuse headache</i>
Population criteria:	<i>Patient must be aged 18 years or older</i>
Prescriber instructions:	<i>Patients who have previously responded to this medication and have in the past met the continuation criteria may recommence treatment under the continuation criteria and do not require re-initiation.</i>
Administrative Advice	<i>No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised.</i>

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
FREMANEZUMAB 225 mg in 1.5mL solution for injection, 150 mg/1mL x 1 pre-filled pen	3	3	1	Published: \$ [REDACTED] Effective: \$ [REDACTED]	Ajovy®, TEVA

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	<i>Chronic</i>
Severity:	-
Condition	<i>Migraine</i>
PBS Indication:	<i>Chronic migraine</i>
Treatment phase:	<i>Subsequent continuing treatment (3 monthly dosing)</i>
Restriction: 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
Treatment criteria:	<i>Must be treated by, or in consultation with a specialist neurologist; or Must be treated by, or in consultation with a specialist pain medicine physician accredited or experienced in treating headache</i>

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Clinical criteria:	<i>Patient must have previously received PBS-subsidised treatment with this drug for this condition under the First continuing treatment restriction AND Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine days per month in order to be eligible for continuing PBS-subsidised treatment AND The treatment must not be in combination with PBS-subsidised botulinum toxin type A or a PBS-subsidised anti-calcitonin gene-related peptide (anti-CGRP) drug for chronic migraine AND The treatment must be administered on a 3 monthly dosing schedule AND Patient must continue to be appropriately managed for medication overuse headache</i>
Population criteria:	<i>Patient must be aged 18 years or older</i>
Prescriber instructions:	-
Administrative Advice	<i>No increase in the maximum quantity or number of units may be authorised No increase in the maximum number of repeats may be authorised.</i>

- 2.1 The submission requested a special pricing arrangement with an effective price at a discount to the proposed published price and also proposed to [REDACTED].
- 2.2 The submission requested initial treatment and first continuing treatment be prescribed by a neurologist or pain specialist, with subsequent continuing treatment able to be prescribed by, or in conjunction with, a neurologist or pain specialist. The PBAC agreed with the Secretariat that pain specialist could be defined more precisely as “a specialist pain medicine physician accredited or experienced in treating headache”. The PBAC recalled it had recommended initial treatment with galcanezumab be prescribed by neurologists with continuing treatment prescribed by, or in conjunction with, a neurologist (paragraph 8.1, galcanezumab Public Summary Document (PSD), July 2019 PBAC meeting).
- 2.3 The proposed restriction was narrower than the TGA indication, which does not restrict treatment based on migraine frequency (i.e. episodic or chronic), migraine characteristics, or prior therapies. The PBAC considered there was a high risk of use outside of the restriction i.e. among patients with episodic migraine, patients with chronic migraine that do not meet the prior therapy requirements and continued use in patients who do not meet the required response criteria but who have experienced an improvement in migraine symptoms on fremanezumab (partial responders).
- 2.4 The submission requested grandfathering provisions for patients treated under the sponsor’s product familiarisation program (expected to commence in November 2019). The PBAC considered grandfathered patients should be eligible for PBS subsidised treatment under the proposed initial restriction criteria and therefore a separate grandfather restriction would not be required.
- 2.5 The proposed maximum quantity and repeats provide 3 months of initial treatment and 6 months of continuing treatment at the recommended doses of 225 mg every

month or 675 mg (given as 3 x 225 mg injections) every three months. Patients treated with monthly dosing would pay one co-payment per month of treatment whereas patients treated with three monthly dosing would pay one co-payment per three months of treatment. The Secretariat noted that if patients treated with the monthly dosing schedule were prescribed under the three monthly criteria (to reduce the number of co-payments), it could result in wastage (e.g. if the first injection is not tolerated) or quality use of medicine (QUM) issues (e.g. if the medication is not stored correctly between doses). The pre-PBAC response suggested limiting initial treatment to the monthly regimen and having the three monthly regimen available only for continuing treatment may limit the wastage and QUM concerns

- 2.6 The proposed restriction for initial treatment included the following population criteria: “A maximum of 1 initiation cycle of 3 injections will be authorised under this restriction in a lifetime. Patients who have previously responded to this medication and have in the past met the continuation criteria may recommence treatment under the continuation criteria and do not require re-initiation.” The PBAC noted this criteria was proposed to ensure patients are only treated under the initial restriction once per lifetime as the [REDACTED].
- 2.7 The dispensed price for maximum quantity (DPMQ) in the submission was calculated incorrectly for both the monthly and 3 monthly treatment regimen with incorrect wholesaler mark-ups and administration, handling and infrastructure fees applied to both listings which resulted in a small overestimate of the DPMQ. This error has not been corrected in these minutes.

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

3 Background

Registration status

- 3.1 **TGA status at time of PBAC consideration:** fremanezumab was TGA registered on 17 September 2019 for the “preventive treatment of migraine in adults”.
- 3.2 Fremanezumab was submitted under the TGA/PBAC parallel process. At the time of evaluation, the TGA Round 1 and 2 clinical evaluation, the Delegate’s overview and the ACM minutes were available.
- 3.3 The recommended dose of fremanezumab is 225 mg monthly or 675 mg every three months by subcutaneous injection. The PBAC noted the pivotal clinical evidence for fremanezumab included a loading dose of 675 mg for patients receiving monthly treatment but this loading dose is not included in the dosing recommendations in the product information. The PBAC noted the dosing interval in the fremanezumab clinical trial was 4 weekly and 12 weekly and the dose recommendation in the product information is monthly and three monthly.

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

4 Population and disease

- 4.1 Migraine is a chronic neurological condition characterised by recurrent episodes of headache which are typically unilateral, pulsating, and associated with moderate or severe pain. The headaches are exacerbated by routine physical activity and are often associated with other symptoms such as photophobia, phonophobia, nausea, and vomiting. Migraine episodes can significantly impair functional ability at work or school, at home, and in social situations (American Headache Society Consensus Statement 2018).
- 4.2 Chronic migraine is defined as a headache occurring on 15 or more days per month for more than 3 months, which, on at least 8 days per month, have the features of migraine headache (International Classification of Headache Disorders 3rd edition).
- 4.3 A systematic review of the global prevalence of chronic migraine in 2010 reported a prevalence of chronic migraine ranging from 0 to 5.1%, with estimates typically in the range of 1.4 to 2.2%. The prevalence of chronic migraine was 2.5 to 6.5 times higher in women (1.7 to 4.0%) than in men (0.6 to 0.7%) among three studies that reported gender-specific estimates¹. The DUSC previously considered that the prevalence of chronic migraine in Australia is likely to be approximately 400,000 patients (paragraph 4.3, erenumab PSD, March 2019 PBAC meeting).
- 4.4 The submission positioned fremanezumab as a treatment option for the following three groups of patients:
- Patients who are eligible to be treated with Botox but are either unwilling due to a needle or Botox phobia, or who are unable to access treatment from a Botox-accredited neurologist or who have contraindications to Botox (referred to in the submission as the 'Botox ruled out' population). The PBAC noted there are very few contraindications to treatment with Botox (hypersensitivity to ingredients, patients with myasthenia gravis or Eaton Lambert Syndrome).
 - Patients who are eligible and willing to be treated with Botox.
 - Patients who have tried and failed or are intolerant to Botox.

5 Comparator

- 5.1 The submission nominated Botox as the main comparator for the population eligible for and willing to be treated with Botox. The PBAC considered that Botox was a reasonable comparator in this population.
- 5.2 The submission nominated BSC as the main comparator for the populations for whom Botox had been ruled out (as defined in paragraph 4.4) or who have previously failed treatment with Botox. The PBAC considered BSC may be a reasonable comparator for

¹ Natoli, J. L., A. Manack, B. Dean, Q. Butler, C. C. Turkel, L. Stovner and R. B. Lipton (2010). "Global prevalence of chronic migraine: a systematic review." *Cephalalgia* 30(5): 599-609.

these populations but that Botox was also an appropriate comparator given the lack of clarity regarding the Botox ruled out population.

- 5.3 The submission did not adequately describe the distinction between patients who would be considered Botox eligible and those who would be considered Botox unsuitable (Botox ruled out). The PBAC considered the Botox eligible and Botox ruled out populations were not well defined and the number of patients within each was highly uncertain.
- 5.4 The submission nominated erenumab and galcanezumab as secondary comparators. Galcanezumab received a positive recommendation for the treatment of patients with chronic migraine at the July 2019 PBAC meeting. Erenumab for chronic migraine had previously been considered by the PBAC in July 2018 and March 2019, and was withdrawn prior to consideration at the November 2019 meeting. The Economics Sub-Committee (ESC) noted fremanezumab and galcanezumab were both CGRP ligand antagonists while erenumab had a slightly different mechanism of action (CGRP receptor antagonist).

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. A neurologist experienced in the treatment of headache presented a clinical case study and discussed the natural history of the disease, how the drug would be used in practice, and addressed other matters in response to the Committee's questions. The clinician explained the treatments and challenges for patients with chronic migraine, and highlighted that the population most in need of anti-CGRP drugs was the Botox intolerant or ineffective population, who had failed three or more preventative therapies. The clinician clarified that responses to the anti-CGRP medicines were highly individualised. The PBAC considered that the hearing was informative but did not add substantively to the evidence presented in the submission.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (57), health care professionals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with fremanezumab including the ability to return to work, fewer side effects and a greater reduction in migraine days compared to other treatments, and improvement in quality of life.
- 6.3 The PBAC noted the advice received from Migraine Australia and the Australian and New Zealand Headache Society clarifying the likely use of fremanezumab in clinical practice. The PBAC specifically noted the advice that the use of fremanezumab may

provide more options for patients who do not respond to Botox and other anti-CGRP drugs, provide greater flexibility with monthly and quarterly dosing, fewer side effects compared to existing preventative therapies, and improved quality of life in some patients.

Clinical trials

6.4 The clinical evidence for fremanezumab was based on the results of Study 30068, which enrolled patients with episodic (n=329) and chronic (n=509) migraine. The submission excluded the registration study for fremanezumab in chronic migraine (Study 30049, n=1,130) on the basis that it did not include patients who were representative of the requested PBS population (patients with ≥ 3 treatment failures).

6.5 The submission was based on a series of comparisons of fremanezumab (based on Study 30068) and the nominated comparators in patients with chronic migraine and a post hoc subgroup of patients with ≥ 3 prior treatment failures:

- Head-to-head comparison of fremanezumab versus placebo.
- Indirect comparison of fremanezumab and Botox (PREEMPT1 and PREEMPT2).
- Indirect comparison of fremanezumab and erenumab (Study 295).
- Indirect comparison of fremanezumab and galcanezumab (REGAIN).

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Fremanezumab trials		
Study 30068 (NCT03308968)	A multicenter, randomized, double-blind, parallel-group, placebo-controlled study with an open-label period to evaluate the efficacy and safety of fremanezumab for the prophylactic treatment of migraine in patients with inadequate response to prior preventive treatments.	Clinical Study Report (interim), 6 March 2019.
	Ferrari MD, Diener HC, Ning X, Galic M et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. ^a	The Lancet (2019); Epub ahead of print.
Study 30051 (NCT02638103)	A multicenter, randomized, double-blind, parallel-group study evaluating the long-term safety, tolerability, and efficacy of subcutaneous administration of fremanezumab (TEV-48125) for the preventive treatment of migraine.	Clinical Study Report (interim), 18 December 2017.
	Silberstein SD, Lipton RB, Diamond ML, Cohen JM et al. Achievement of response over time with fremanezumab in the treatment of chronic and episodic migraine.	Headache 2018; 58(8): 1300-1301.
Botulinum toxin A trials		
PREEMPT1	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.
PREEMPT2	Diener HC, Dodick DW, Aurora SK, Turkel CC 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.

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Trial ID	Protocol title/ Publication title	Publication citation
PREEMPT Pooled	Dodick DW, Turkel CC, DeGryse RE, Aurora SK et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program.	<i>Headache</i> 2010; 50(6): 921-936.
	Aurora SK, Winner P, Freeman MC, Spierings EL et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program.	<i>Headache</i> 2011; 51: 1358-1373.
	CADTH Clinical Review Report for Botox.	July 2015
	Scottish Medicines Consortium. Botulinum toxin SMC No. (692/11) 2nd Resubmission Advice.	2017
	National Institute for Health and Care Excellence (NICE) Single Technology Appraisal. Erenumab for preventing migraine [ID1188] Committee Papers.	2018
Erenumab trials		
Study 295 (NCT02066415)	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.	<i>The Lancet Neurology</i> 2017; 16(6): 425-434.
	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.	<i>Cephalalgia</i> 2018, 38(10): 1611–1621.
	National Institute for Health and Care Excellence (NICE) Single Technology Appraisal. Erenumab for preventing migraine [ID1188] Committee Papers.	2018
Study 295 long-term safety extension (NCT02174861)	Tepper, S, Ashina M, Reuter U, Brandes JL et al. Assessment of the long-term safety and efficacy of erenumab during open-label treatment of subjects with chronic migraine.	<i>The Journal of Headache and Pain</i> ; 2018, 19(Suppl 1):80.
Galcanezumab trials		
REGAIN (NCT02614261)	Detke HC, Goadsby PJ, Wang S, Friedman D et al. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study.	<i>Neurology</i> 2018; 91:e2211-e2221.
	Dell'Agnello G, Tockhorn-Heidenreich A, Zhang Q, Ruff DD et al. Efficacy of galcanezumab in patients who failed prior preventive treatments for migraine: results from EVOLVE-1, EVOLVE-2 and REGAIN studies: O19.	<i>The Journal of Headache and Pain</i> 2018, 19(Suppl 1):80.
	Ruff DD, Ford JH, Tockhorn-Heidenreich A, Sexson M et al. Efficacy of galcanezumab in patients with chronic migraine and a history of preventive treatment failure.	<i>Cephalalgia</i> 2019; 39(8):931-944.

Selected citations relating to conference abstracts omitted.

Source: Table 2.5, pp38-41 of the submission.

^a Publication identified during the evaluation.

6.7 The key features of the direct randomised trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Fremanezumab versus placebo						
Study 30068	838 (chronic migraine subgroup n=509; chronic migraine with ≥3 prior treatments subgroup n=293)	R, DB, MC 12 weeks	Low ^a	Chronic and episodic migraine; failed 2 to 4 classes of preventive migraine medications	Change in monthly migraine days (primary); change in monthly headache days; ≥50% reduction in monthly migraine days.	Monthly migraine days; ≥50% reduction in monthly migraine days
Botox versus placebo						
PREEMPT1 and PREEMPT2 pooled analysis	1,384 (≥3 prior treatments n=479)	R, DB, MC 24 weeks	Low	Chronic migraine	Change in frequency of headache episodes (PREEMPT1 primary); change in monthly headache days (PREEMPT2 primary); change in monthly migraine days.	Not used
Erenumab versus placebo						
Study 295	677 (≥3 prior treatments n=232)	R, DB, MC 12 weeks	Low	Chronic migraine; excluded patients with no therapeutic response >3 prior treatments	Change in monthly migraine days (primary); ≥50% reduction in monthly migraine days.	Not used
Galcanezumab versus placebo						
REGAIN	1,113 (≥3 prior treatments n=199)	R, DB, MC 3 months	Low	Chronic migraine; excluded patients who had failed >3 different medication classes.	Change in monthly migraine days (primary); ≥50% reduction in monthly migraine days.	Not used

Source: Table 2.13, pp62-65; Table 2.24, pp95-96; Table 2.26, pp97-98 of the submission; Table 3-2 pp16-17; Table 4-2, pp33-34 of Attachment 5 of the submission; pp2212-2213 of Detke et al. (2018); pp427-428 of Tepper et al. (2017).

Abbreviations: DB, double-blind; MC, multi-centre; R, randomised.

^a Outcomes for the chronic migraine subgroup with ≥3 prior treatments were not pre-specified and were at high risk of bias.

6.8 The submission provided an abridged interim clinical study report for Study 30068 which reported the combined results for episodic and chronic migraine patients. The submission also provided additional results for the chronic migraine subgroup, and the subgroup of chronic migraine patients with ≥3 prior treatment failures. Analyses based on the subgroup of chronic migraine patients with ≥3 treatment failures were not pre-specified in the trial.

6.9 The submission used results for the subgroup of chronic migraine patients treated with fremanezumab in Study 30068 to conduct indirect comparisons versus PREEMPT1/2, Study 295 and REGAIN. The submission also conducted indirect comparisons based on the subgroup of chronic migraine patients with ≥3 prior treatment failures. These post hoc analyses were considered to be at high risk of bias. The Pre-Sub-Committee Response (PSCR) noted that the PBAC had previously made positive recommendations based on subgroup analyses of patients with ≥3 prior

treatment failures in the key Botox and galcanezumab studies, despite there also being a high risk of bias with the post-hoc analyses.

- 6.10 All trials permitted the use of medications for the management of acute migraine episodes. Medications used for the treatment of acute episodes may have influenced the frequency of migraine episodes reported in the trials. Differences between the trials in the use of acute migraine treatments may bias the results of the indirect comparisons.
- 6.11 The following issues are likely to have affected the reliability of the indirect comparisons presented in the submission:
- The proportion of patients with ≥ 3 prior treatment failures varied substantially between trials, with █% in Study 30068, 35% in PREEMPT1/2 and Study 295, and 18% in REGAIN.
 - There were differences in the definitions of prior treatment failure, and differences in the prior treatment medicine categories specified in each trial. The PBAC considered it was unclear to what extent the subgroups across all the trials identified patients who would be treated under the proposed PBS criteria i.e. patients who have had an inadequate response, intolerance or a contraindication to ≥ 3 prophylactic migraine medications (namely propranolol, amitriptyline, pizotifen, candesartan, verapamil, nortriptyline, sodium valproate or topiramate).
 - Around 15% of patients in REGAIN received treatment with concurrent preventive therapy during the trial (topiramate or propranolol).
 - In Study 30068, Study 295 and REGAIN, the placebo intervention consisted of 1 to 3 subcutaneous injections, whereas in PREEMPT1/2, the placebo intervention consisted of intramuscular injections to 31 to 39 sites in the face and neck.
 - Headache/migraine days were based on a headache length of ≥ 30 minutes in REGAIN, whereas Study 30068, PREEMPT1/2, and Study 295 were based on a headache length of ≥ 4 hours.
 - Response was based on a $\geq 50\%$ reduction in monthly headache days in PREEMPT1/2, whereas response was based on a $\geq 50\%$ reduction in monthly migraine days in Study 30068, Study 295 and REGAIN.
 - In the PREEMPT trials, assessments were conducted at 12 and 24 weeks, whereas Study 30068, Study 295 and REGAIN were based on assessment at 12 weeks. Outcome data for the 12-week time point was not available for the subgroup of patients with ≥ 3 prior treatment failures in PREEMPT1/2.
- 6.12 The interim clinical study report for study 30068 presented results from 2076 anti-drug antibody (ADA) samples collected from █ drug-treated patients (chronic and episodic migraine patients). █ out of █ patients (█%) were identified as having a treatment-emergent antidrug antibody response. █ of the █ patients identified as having treatment-emergent anti-drug antibody responses were determined to have

developed neutralising activity in the neutralising antibody assay. The ESC considered that poor adherence to the treatment may increase the likelihood of developing ADAs, and that it was unclear what this likelihood would be in a real world setting with patients who have comorbidities.

Comparative effectiveness

- 6.13 The submission noted that a minimal clinically important difference (MCID) of around 2 to 3 days for monthly headache days had previously been accepted by the PBAC. The PBAC previously considered that a reduction of 2-3 headache days per month could be considered to be a clinically important benefit (Section 12, p.5, Botox PSD, July 2012 PBAC meeting).
- 6.14 The submission proposed an MCID of at least 2 days for monthly migraine days, based on the assumption that the MCID for migraine days is likely to be the same or very similar to the MCID for headache days.
- 6.15 The submission claimed that, based on a headache MCID of at least 2-3 days, a reasonable non-inferiority margin for monthly migraine days would be around 2 days.
- 6.16 Outcomes for Study 30068 were based on the change in migraine/headache days from baseline over the 12-week double-blind treatment period. The submission also presented results for the change from baseline to the final 4 weeks of the double-blind treatment period. These results were used in the indirect comparisons versus Botox and erenumab for consistency with the reported outcomes in PREEMPT1/2 and Study 295.

Fremanezumab versus placebo

- 6.17 Results of the comparison between fremanezumab and placebo for Study 30068 based on the chronic migraine population are summarised in Table 4.

Table 4: Results for key outcomes of Study 30068 for the chronic migraine population

Outcome/treatment arm	Fremanezumab		Placebo (N=167)		Mean difference (95% CI)
	Baseline mean (SD)	LSM change (95% CI)	Baseline mean (SD)	LSM change (95% CI)	
Change from baseline in monthly migraine days					
FREM 225 mg 4-weekly (N=173)	■ (■)	-4.5 (-5.39, -3.61)	■ (■)	-0.7 (-1.64, 0.20)	-3.8 (-4.76, -2.80)
FREM 675 mg 12-weekly (N=169)	■ (■)	-3.9 (-4.79, -2.99)	■ (■)	-0.7 (-1.64, 0.20)	-3.2 (-4.16, -2.18)
Fremanezumab 225 mg 4-weekly versus fremanezumab 675 mg 12-weekly					-0.6 (-1.59, 0.37)
Change from baseline in monthly headache days					
FREM 225 mg 4-weekly (N=173)	■ (■)	(■, ■)	■ (■)	(■, ■)	■ (■, ■)
FREM 675 mg 12-weekly (N=169)	■ (■)	(■, ■)	■ (■)	(■, ■)	■ (■, ■)
	Fremanezumab n with event/N (%)		Placebo n with event/N (%)		Odds ratio (95% CI)
Proportion of patients with ≥50% reduction in monthly average number of migraine days					
FREM 225 mg 4-weekly (N=173)	■/173 (■)		■/167 (■)		■ (■, ■)
FREM 675 mg 12-weekly (N=169)	■/169 (■)		■/167 (■)		■ (■, ■)

Bolded results indicate a statistically significant difference.

Source: Table 2.31, pp113-114; Table 2.32, pp115-116; Table 2.35, pp119-120 of the submission.

Abbreviations: CI, confidence interval; FREM, fremanezumab; LSM, least squares mean; SD, standard deviation.

- 6.18 Compared to placebo, treatment with fremanezumab 225 mg every 4 weeks was associated with statistically significant improvements in monthly migraine days (mean difference: -3.8; 95% CI: -4.76, -2.80), monthly headache days (mean difference: ■; 95% CI: ■, ■), and the proportion of patients with a ≥50% reduction in monthly migraine days (odds ratio: ■; 95% CI: ■, ■). The upper confidence interval for the change in monthly migraine days (-2.80 days) was greater than the proposed MCID of at least 2 days.
- 6.19 Compared to placebo, treatment with fremanezumab 625 mg every 12 weeks was associated with statistically significant improvements in monthly migraine days (mean difference: -3.2 days; 95% CI: -4.16, -2.18), monthly headache days (mean difference: ■ days; 95% CI: ■, ■), and the proportion of patients with a ≥50% reduction in monthly migraine days (odds ratio: ■; 95% CI: ■, ■). The upper confidence interval for the change in monthly migraine days (-2.18 days) was greater than the proposed MCID of at least 2 days.
- 6.20 The reductions in monthly migraine days in the fremanezumab 675 mg 12-weekly arm were numerically smaller across the monthly migraine days, monthly headache days, and responder outcomes, compared to the fremanezumab 225 mg 4-weekly arm. These differences may be due to the inclusion of the 675 mg loading dose in the 225 mg 4-weekly treatment regimen, which resulted in a higher cumulative dose of fremanezumab (1,125 mg) over the 12-week double-blind treatment period, compared to the fremanezumab 12-weekly treatment arm (675 mg). However, a

comparison of fremanezumab 225 mg 4-weekly and fremanezumab 675 mg 12-weekly for the outcome of change in mean monthly migraine days indicated that there was no statistically significant difference.

- 6.21 Treatment with fremanezumab 225 mg every 4 weeks and 675 mg every 12 weeks was associated with statistically significant improvements in the Migraine-Specific Quality of Life Questionnaire (MSQ) role function restrictive, role function preventive, and role function emotional scores. The results did not meet the nominated MCIDs for role restrictive, role preventive, and emotional function.
- 6.22 Treatment with fremanezumab 225 mg every 4 weeks and 675 mg every 12 weeks was associated with statistically significant improvements in the Headache Impact Test (HIT-6) compared to placebo. The 675 mg 12-weekly arm did not meet the nominated MCID for improvement in the HIT-6.
- 6.23 The results of the comparison between fremanezumab and placebo for Study 30068 for the chronic migraine population with ≥3 prior treatment failures are summarised in Table 5.

Table 5: Results for key outcomes of Study 30068 for the subgroup with ≥3 prior treatments

Outcome/treatment arm	Fremanezumab		Placebo		Mean difference (95% CI)
	Baseline mean (SD)	LSM change (95% CI)	Baseline mean (SD)	LSM change (95% CI)	
Change from baseline in monthly migraine days					
FREM 225 mg 4-weekly	█ (N=█)	█ (█, █)	█ (N=█)	█ (█, █)	█ (█, █)
FREM 675 mg 12-weekly	█ (N=█)	█ (█, █)	█ (N=█)	█ (█, █)	█ (█, █)
Fremanezumab 225 mg 4-weekly versus fremanezumab 675 mg 12-weekly					█ (█, █)
Change from baseline in monthly headache days					
FREM 225 mg 4-weekly	█ (N=█)	█ (█, █)	█ (N=█)	█ (█, █)	█ (█, █)
FREM 675 mg 12-weekly	█ (N=█)	█ (█, █)	█ (N=█)	█ (█, █)	█ (█, █)
	Fremanezumab n with event/N (%)		Placebo n with event/N (%)		Odds ratio (95% CI)
Proportion of patients with ≥50% reduction in monthly average number of migraine days					
FREM 225 mg 4-weekly	█ (█)		█ (█)		█ (█, █)
FREM 675 mg 12-weekly	█ (█)		█ (█)		█ (█, █)

Bolded results indicate a statistically significant difference.

Source: Table 2.31, pp113-114; Table 2.32, pp115-116; Table 2.35, pp119-120 of the submission.

Abbreviations: CI, confidence interval; FREM, fremanezumab; LSM, least squares mean; SD, standard deviation.

- 6.24 Compared to placebo, treatment with fremanezumab 225 mg every 4 weeks was associated with statistically significant improvements in monthly migraine days (mean difference: █; 95% CI: █, █), monthly headache days (mean difference: █; 95% CI: █, █), and the proportion of patients with a ≥50% reduction in monthly migraine days (odds ratio: █; 95% CI: █, █). The upper confidence interval for the change in monthly migraine days (█ days) was less than the proposed MCID of at least 2 days.

6.25 Compared to placebo, treatment with fremanezumab 625 mg every 12 weeks was associated with statistically significant improvements in monthly migraine days (mean difference: [redacted]; 95% CI: [redacted], [redacted]), monthly headache days (mean difference: [redacted] days; 95% CI: [redacted], [redacted]), and the proportion of patients with a ≥50% reduction in monthly migraine days (odds ratio: [redacted]; 95% CI: [redacted], [redacted]). The upper confidence interval for the change in monthly migraine days ([redacted] days) was less than the proposed MCID of at least 2 days.

Fremanezumab versus Botox

6.26 Table 6 presents the results of the indirect comparison of fremanezumab (12 weeks) and Botox (24 weeks) for the full chronic migraine population.

Table 6: Indirect comparisons for fremanezumab (12 weeks) versus Botox (24 weeks) for the full chronic migraine population

Trial	Mean change from baseline (SE) in monthly migraine days			Mean difference (95% CI)
	Fremanezumab	Placebo	Botox	
Study 30068 FREM 4-weekly	N= 173 [redacted] ([redacted])	N=167 [redacted] ([redacted])	-	[redacted] ([redacted])
Study 30068 FREM 12-weekly	N= 169 [redacted] ([redacted])	N=167 [redacted] ([redacted])	-	[redacted] ([redacted])
Pooled PREEMPT trials (24 weeks)	-	N=688 -6.2 (0.26)	N=696 -8.2 (0.25)	-2.0 (NR)
Indirect mean difference fremanezumab 4-weekly versus Botox				[redacted] ([redacted], [redacted])
Indirect mean difference fremanezumab 12-weekly versus Botox				[redacted] ([redacted], [redacted])
Trial	Mean change from baseline (SE) in monthly headache days			Mean difference (95% CI)
	Fremanezumab	Placebo	Botox	
Study 30068 FREM 4-weekly	N= 173 [redacted] ([redacted])	N=167 [redacted] ([redacted])	-	[redacted] ([redacted])
Study 30068 FREM 12-weekly	N= 169 [redacted] ([redacted])	N=167 [redacted] ([redacted])	-	[redacted] ([redacted])
Pooled PREEMPT trials (12 weeks)	-	N=688 -6.6 (0.25)	N=696 -8.4 (0.25)	-1.8 (NR)
Indirect mean difference fremanezumab 4-weekly versus Botox				[redacted] ([redacted], [redacted])
Indirect mean difference fremanezumab 12-weekly versus Botox				[redacted] ([redacted], [redacted])
Trial	≥50% reduction in monthly headache/migraine days n with event/N (%)			Odds ratio (95% CI)
	Fremanezumab	Placebo	Botox	
Study 30068 FREM 4-weekly	[redacted]/173 ([redacted]%)	[redacted]/167 ([redacted]%)	-	[redacted] ([redacted])
Study 30068 FREM 12-weekly	[redacted]/169 ([redacted]%)	[redacted]/167 ([redacted]%)	-	[redacted] ([redacted])
Pooled PREEMPT trials (24 weeks)	-	222/693 (32.0%)	286/685 (41.8%)	1.52 (NR)
Indirect odds ratio fremanezumab 4-weekly versus Botox				[redacted] ([redacted], [redacted])
Indirect odds ratio fremanezumab 12-weekly versus Botox				[redacted] ([redacted], [redacted])

Bolded results indicate a statistically significant difference.

Source: Table 2.57, p.152; Table 2.58, p.154; Table 2.59, pp155-156 of the submission.

Abbreviations: CI, confidence interval; FREM, fremanezumab; NR, not reported; SE, standard error.

6.27 Treatment with fremanezumab 225 mg every 4 weeks was associated with a statistically significant improvement in monthly migraine days, monthly headache

days, and the proportion of patients with a ≥50% response compared to Botox (24-week assessment).

- 6.28 There were no statistically significant differences between fremanezumab 675 mg every 12 weeks and Botox (24-week assessment).
- 6.29 Table 7 presents the results of the indirect comparison of fremanezumab (12 weeks) and Botox (24 weeks) for the subgroup of chronic migraine patients with ≥3 prior treatment failures.

Table 7: Indirect comparisons of fremanezumab (12 weeks) versus Botox (24 weeks) for the subgroup of chronic migraine patients with ≥3 prior treatments

Trial	Mean change from baseline (SE) in monthly migraine days			Mean difference (95% CI)
	Fremanezumab	Placebo	Botox	
Study 30068 FREM 4-weekly	N= [redacted] ([redacted])	N= [redacted] ([redacted])	-	[redacted] ([redacted])
Study 30068 FREM 12-weekly	N= [redacted] ([redacted])	N= [redacted] ([redacted])	-	[redacted] ([redacted])
Pooled PREEMPT trials (24 weeks)	-	N=248 -4.3 (NR)	N=231 -7.1 (NR)	-2.8 (NR)
Indirect mean difference fremanezumab 4-weekly versus Botox				[redacted] ([redacted])
Indirect mean difference fremanezumab 12-weekly versus Botox				[redacted] ([redacted])
Trial	Mean change from baseline (SE) in monthly headache days			Mean difference (95% CI)
	Fremanezumab	Placebo	Botox	
Study 30068 FREM 4-weekly	N= [redacted] ([redacted])	N= [redacted] ([redacted])	-	[redacted] ([redacted])
Study 30068 FREM 12-weekly	N= [redacted] ([redacted])	N= [redacted] ([redacted])	-	[redacted] ([redacted])
Pooled PREEMPT trials (12 weeks)	-	N=248 -4.7 (NR)	N=231 -7.4 (NR)	-2.7 (NR)
Indirect mean difference fremanezumab 4-weekly versus Botox				[redacted] ([redacted])
Indirect mean difference fremanezumab 12-weekly versus Botox				[redacted] ([redacted])
Trial	≥50% reduction in monthly migraine/headache days n with event/N (%)			Odds ratio (95% CI)
	Fremanezumab	Placebo	Botox	
Study 30068 FREM 4-weekly	[redacted] ([redacted])	[redacted] ([redacted])	-	[redacted] (NR)
Study 30068 FREM 12-weekly	[redacted] ([redacted])	[redacted] ([redacted])	-	[redacted] (NR)
Pooled PREEMPT trials (24 weeks)	-	[redacted] ([redacted])	85/231 (36.8%)	1.94 (NR)
Indirect risk ratio fremanezumab 4-weekly versus Botox				[redacted] ([redacted])
Indirect risk ratio fremanezumab 12-weekly versus Botox				[redacted] ([redacted])

Bolded results indicate a statistically significant difference.

Source: Table 2.57, p.152; Table 2.58, p.154; Table 2.59, pp155-156 of the submission.

Abbreviations: CI, confidence interval; NR, not reported; SE, standard error.

- 6.30 There were no statistically significant differences between fremanezumab 225 mg every 4 weeks or fremanezumab 675 mg every 12 weeks and Botox (24 weeks) for the change in monthly migraine days, change in monthly headache days, or the proportion of patients with a ≥50% response. The upper 95% confidence interval for the fremanezumab 675 mg 12-weekly subgroup comparison ([redacted]) exceeded the nominated non-inferiority margin of 2 days for change in monthly migraine days.

Fremanezumab versus erenumab

6.31 Table 8 presents the results of the indirect comparison of fremanezumab and erenumab for the full chronic migraine population.

Table 8: Indirect comparisons of fremanezumab versus erenumab for the full chronic migraine population

Trial	Mean change from baseline (SE) in monthly migraine days			Mean difference (95% CI)
	Fremanezumab	Placebo	Erenumab	
Study 30068 FREM 4-weekly	N= 173 ■ (■)	N=167 ■ (■)	-	■ (■)
Study 30068 FREM 12-weekly	N= 169 ■ (■)	N=167 ■ (■)	-	■ (■)
Study 295 EREN 70 mg	-	N=281 -4.24 (0.38)	N=188 -6.63 (0.45)	-2.39 (NR)
Study 295 EREN 140 mg	-	N=281 -4.24 (0.38)	N=187 -6.53 (0.50)	-2.29 (NR)
Indirect mean difference fremanezumab 4-weekly versus erenumab 70 mg				■ (■)
Indirect mean difference fremanezumab 12-weekly versus erenumab 70 mg				■ (■)
Indirect mean difference fremanezumab 4-weekly versus erenumab 140 mg				■ (■)
Indirect mean difference fremanezumab 12-weekly versus erenumab 140 mg				■ (■)
	≥50% reduction in monthly migraine days n with event/N (%)			Odds ratio (95% CI)
	Fremanezumab	Placebo	Erenumab	
Study 30068 FREM 4-weekly	■/173 (■%)	■/167 (■%)	-	■ (■)
Study 30068 FREM 12-weekly	■/169 (■%)	■/167 (■%)	-	■ (■)
Study 295 EREN 70 mg	-	66/281 (23.5%)	75/188 (39.9%)	2.16 (NR)
Study 295 EREN 140 mg	-	66/281 (23.5%)	77/187 (41.2%)	2.28 (NR)
Indirect risk ratio fremanezumab 4-weekly versus erenumab 70 mg				■ (■)
Indirect risk ratio fremanezumab 12-weekly versus erenumab 70 mg				■ (■)
Indirect risk ratio fremanezumab 4-weekly versus erenumab 140 mg				■ (■)
Indirect risk ratio fremanezumab 12-weekly versus erenumab 140 mg				■ (■)

Bolded results indicate a statistically significant difference.

Source: Table 3.5, p.22; Table 3.6, p.23 of Attachment 5 of the submission.

Abbreviations: CI, confidence interval; EREN, erenumab; FREM, fremanezumab; NR, not reported; SE, standard error.

6.32 There were no statistically significant differences for any of the included indirect comparisons.

6.33 Table 9 presents the results of the indirect comparison of fremanezumab and erenumab for the subgroup of chronic migraine patients with ≥3 prior treatment failures.

Table 9: Indirect comparisons for fremanezumab versus erenumab for the subgroup of chronic migraine patients with ≥3 prior treatments

Trial	Mean change from baseline (SE) in monthly migraine days			Mean difference (95% CI)
	Fremanezumab	Placebo	Erenumab	
Study 30068 FREM 4-weekly	N= [redacted] ([redacted])	N= [redacted] ([redacted])	[redacted]	[redacted] ([redacted])
Study 30068 FREM 12-weekly	N= [redacted] ([redacted])	N= [redacted] ([redacted])	[redacted]	[redacted] ([redacted])
Study 295 EREN 70 mg	-	N=98 -2.8 (0.6)	NR	-2.5 (-4.3, -0.8)
Study 295 EREN 140 mg	-	N=98 -2.8 (0.6)	-7.0 (0.9)	-4.1 (-5.8, -2.3)
Indirect mean difference fremanezumab 4-weekly versus erenumab 70 mg				[redacted] ([redacted])
Indirect mean difference fremanezumab 12-weekly versus erenumab 70 mg				[redacted] ([redacted])
Indirect mean difference fremanezumab 4-weekly versus erenumab 140 mg				[redacted] ([redacted])
Indirect mean difference fremanezumab 12-weekly versus erenumab 140 mg				[redacted] ([redacted])
	≥50% reduction in monthly migraine days n with event/N (%)			Odds ratio (95% CI)
	Fremanezumab	Placebo	Erenumab	
Study 30068 FREM 4-weekly	[redacted] / [redacted] ([redacted] %)	[redacted] / [redacted] ([redacted] %)	-	[redacted] ([redacted])
Study 30068 FREM 12-weekly	[redacted] / [redacted] ([redacted] %)	[redacted] / [redacted] ([redacted] %)	-	[redacted] ([redacted])
Study 295 EREN 70 mg	-	15/98 (15.3%)	23/69 (34.8%)	2.95 (NR)
Study 295 EREN 140 mg	-	15/98 (15.3%)	25/65 (38.5%)	3.47 (NR)
Indirect risk ratio fremanezumab 4-weekly versus erenumab 70 mg				[redacted] ([redacted])
Indirect risk ratio fremanezumab 12-weekly versus erenumab 70 mg				[redacted] ([redacted])
Indirect risk ratio fremanezumab 4-weekly versus erenumab 140 mg				[redacted] ([redacted])
Indirect risk ratio fremanezumab 12-weekly versus erenumab 140 mg				[redacted] ([redacted])

Bolded results indicate a statistically significant difference.

Source: Table 3.5, p.22; Table 3.6, p.23 of Attachment 5 of the submission.

Abbreviations: CI, confidence interval; EREN, erenumab; FREM, fremanezumab; NR, not reported; SE, standard error.

6.34 There were no statistically significant differences for any of the included indirect comparisons. The upper 95% confidence interval for the fremanezumab 675 mg 12-weekly versus erenumab 70 mg and 140 mg comparisons, and for the fremanezumab 225 mg 4-weekly comparison versus erenumab 140 mg exceeded the nominated non-inferiority margin of 2 days for the change in monthly migraine days.

Fremanezumab versus galcanezumab

6.35 Table 10 presents the results of the indirect comparison of fremanezumab and galcanezumab for the full chronic migraine population.

Table 10: Indirect comparisons for fremanezumab versus galcanezumab (full chronic migraine population)

Trial	Mean change from baseline (SE) in monthly migraine days			Mean difference (95% CI)
	Fremanezumab	Placebo	Galcanezumab	
Study 30068 FREM 4-weekly	N=173 ■ (■)	N=167 ■ (■)	-	■ (■)
Study 30068 FREM 12-weekly	N=169 ■ (■)	N=167 ■ (■)	-	■ (■)
REGAIN GALC 120 mg	-	N=538 -2.7 (0.4)	N=273 -4.8 (0.4)	-2.1 (NR)
Indirect mean difference fremanezumab 4-weekly versus galcanezumab				■ (■)
Indirect mean difference fremanezumab 12-weekly versus galcanezumab				■ (■)
Trial	Mean change from baseline (SE) in monthly headache days			Mean difference (95% CI)
	Fremanezumab	Placebo	Galcanezumab	
Study 30068 FREM 4-weekly	N=173 ■ (■)	N=167 ■ (■)	-	■ (■)
Study 30068 FREM 12-weekly	N=169 ■ (■)	N=167 ■ (■)	-	■ (■)
REGAIN GALC 120 mg	-	N=538 -3.0 (0.4)	N=273 -4.8 (0.4)	■ (■)
Indirect mean difference fremanezumab 4-weekly versus galcanezumab				■ (■)
Indirect mean difference fremanezumab 12-weekly versus galcanezumab				■ (■)
	≥50% reduction in monthly migraine days n with event/N (%)			Odds ratio (95% CI)
	Fremanezumab	Placebo	Galcanezumab	
Study 30068 FREM 4-weekly	■/173 (■%)	■/167 (■%)	-	■ (■)
Study 30068 FREM 12-weekly	■/169 (■%)	■/167 (■%)	-	■ (■)
REGAIN GALC 120 mg	-	83/523 (15.9%)	75/273 (27.4%)	2.01 (NR)
Indirect odds ratio fremanezumab 4-weekly versus galcanezumab				■ (■)
Indirect odds ratio fremanezumab 12-weekly versus galcanezumab				■ (■)

Bolded results indicate a statistically significant difference.

Source: Table 4.5, p.39; Table 4.9, pp41-42 of the submission.

Abbreviations: CI, confidence interval; FREM, fremanezumab; GALC, galcanezumab; NR, not reported; SE, standard error.

- 6.36 Treatment with fremanezumab 225 mg every 4 weeks was associated with a statistically significant improvement in monthly migraine days, monthly headache days and the proportion of patients with a ≥50% reduction in monthly migraine days.
- 6.37 There were no statistically significant differences between fremanezumab 675 mg every 12 weeks and galcanezumab 120mg every 4 weeks for the change in monthly migraine days or monthly headache days, and a marginally statistically significant difference for the proportion of patients with a ≥50% reduction in monthly migraine days.
- 6.38 Table 11 presents the results of the indirect comparison of fremanezumab and galcanezumab for the subgroup of chronic migraine patients with ≥3 prior treatment failures.

Table 11: Indirect comparisons for fremanezumab versus galcanezumab (subgroup with ≥3 prior treatments)

Trial	Mean change from baseline (SE) in monthly migraine days			Mean difference (95% CI)
	Fremanezumab	Placebo	Galcanezumab	
Study 30068 FREM 4-weekly	N= [redacted] ([redacted])	N= [redacted] ([redacted])	-	[redacted] ([redacted])
Study 30068 FREM 12-weekly	N= [redacted] ([redacted])	N= [redacted] ([redacted])	-	[redacted] ([redacted])
REGAIN GALC 120 mg	-	N=103 -0.39 (0.76)	N=36 -5.64 (0.97)	-5.25 (NR)
Indirect mean difference fremanezumab 4-weekly versus galcanezumab				[redacted] ([redacted])
Indirect mean difference fremanezumab 12-weekly versus galcanezumab				[redacted] ([redacted])
	≥50% reduction in monthly migraine days n with event/N (%)			Odds ratio (95% CI)
	Fremanezumab	Placebo	Galcanezumab	
Study 30068 FREM 4-weekly	[redacted] ([redacted])%	[redacted] ([redacted])%	-	[redacted] ([redacted])
Study 30068 FREM 12-weekly	[redacted] ([redacted])%	[redacted] ([redacted])%	-	[redacted] ([redacted])
REGAIN GALC 120 mg	-	NR (6.1%)	NR (29.1%)	6.32 (NR)
Indirect odds ratio fremanezumab 4-weekly versus galcanezumab				[redacted] ([redacted])
Indirect odds ratio fremanezumab 12-weekly versus galcanezumab				[redacted] ([redacted])

Bolded results indicate a statistically significant difference.

Source: Table 4.5, p.39; Table 4.9, pp41-42 of the submission.

Abbreviations: CI, confidence interval; FREM, fremanezumab; GALC, galcanezumab; NR, not reported; SE, standard error.

6.39 There were no statistically significant differences for any of the included indirect comparisons. The upper 95% confidence interval for the fremanezumab 225 mg and 675 mg 12-weekly versus galcanezumab 120 mg monthly comparisons exceeded the nominated non-inferiority margin of 2 days for the change in monthly migraine days.

Comparative harms

6.40 Table 12 presents a summary of adverse events reported in Study 30068 for the full chronic migraine population and the subgroup with ≥3 prior treatment failures.

Table 12: Summary of adverse events reported in Study 30068 for the full chronic migraine population

Event	FREM 225 mg 4-weekly	FREM 675 mg 12-weekly	PBO
Full chronic migraine population			
Any AE, n (%)	██████████ ()	██████████ ()	██████████ ()
Treatment-related AE, n (%)	██████████ ()	██████████ ()	██████████ ()
Serious AE, n (%)	██████████ ()	██████████ ()	██████████ ()
AE leading to withdrawal, n (%)	██████████ ()	██████████ ()	██████████ ()
Deaths, n (%)	0/██████████ (0)	0/██████████ (0)	0/██████████ (0)
Treatment-related AE ≥2%, n (%)			
- Injection site erythema	██████████ ()	██████████ ()	██████████ ()
- Injection site induration	██████████ ()	██████████ ()	██████████ ()
- Injection site pain	██████████ ()	██████████ ()	██████████ ()
- Injection site bruising	██████████ ()	██████████ ()	██████████ ()
- Injection site pruritus	██████████ ()	██████████ ()	██████████ ()
- Fatigue	██████████ ()	██████████ ()	██████████ ()
Subgroup with ≥3 prior treatments			
Any AE, n (%)	██████████ ()	██████████ ()	██████████ ()
Treatment-related AE, n (%)	██████████ ()	██████████ ()	██████████ ()
Serious AE, n (%)	██████████ ()	██████████ ()	██████████ ()
AE leading to withdrawal, n (%)	██████████ ()	██████████ ()	██████████ ()
Deaths, n (%)	██████████ ()	██████████ ()	██████████ ()
Treatment-related AE ≥2%, n (%)			
- Injection site erythema	██████████ ()	██████████ ()	██████████ ()
- Injection site induration	██████████ ()	██████████ ()	██████████ ()
- Injection site pain	██████████ ()	██████████ ()	██████████ ()
- Injection site bruising	██████████ ()	██████████ ()	██████████ ()
- Injection site pruritus	██████████ ()	██████████ ()	██████████ ()
- Fatigue	██████████ ()	██████████ ()	██████████ ()
- Injection site rash	██████████ ()	██████████ ()	██████████ ()
- Injection site discolouration	██████████ ()	██████████ ()	██████████ ()
- Injection site paraesthesia	██████████ ()	██████████ ()	██████████ ()
- Injection site haematoma	██████████ ()	██████████ ()	██████████ ()
- Constipation	██████████ ()	██████████ ()	██████████ ()

Bolded results indicate a statistically significant difference.

Source: Table 2.53, p.141 of the submission; Table 2.56, pp144-145 of the submission.

Abbreviations: AE, adverse event; FREM, fremanezumab; PBO, placebo; URTI, upper respiratory tract infection.

- 6.41 The proportion of patients who experienced any adverse event, a treatment-related adverse event, or a serious adverse event during the double-blind phase of the trial were broadly similar across the included treatment arms. The most commonly reported treatment-related adverse events in the fremanezumab treated patients were injection site erythema, induration, pain, bruising, pruritus, and fatigue.
- 6.42 The submission presented the results of statistical tests to assess for differences in the rates of summary adverse events and individual treatment-related adverse events (≥2%) between fremanezumab and placebo for the full chronic migraine population and for the subgroup of patients with ≥3 prior treatment failures. No statistically significant differences were noted for any of the included comparisons.
- 6.43 The most commonly reported treatment-related adverse events for Botox over the 24-week double-blind phase of PREEMPT1/2 (full trial population) were neck pain (6.7%), muscular weakness (5.5%), eyelid ptosis (3.3%), injection-site pain (3.2%),

headache (2.9%), myalgia (2.6%), musculoskeletal stiffness (2.3%) and musculoskeletal pain (2.2%).

- 6.44 Individual treatment-related adverse events for Study 295 and REGAIN were not reported. The most commonly reported treatment-emergent adverse events among erenumab-treated patients in Study 295 over the 12-week double-blind phase (full trial population) were injection site pain (4%), constipation (0%-4%), muscle spasms (<1%-4%), upper respiratory tract infection (3%), nausea (2%-3%), migraine (2%-3%), and nasopharyngitis (2%-3%).
- 6.45 The most commonly reported treatment-emergent adverse events for patients treated with galcanezumab 120 mg in REGAIN over the 12-week double-blind phase (full trial population) were injection site pain (6%), nasopharyngitis (6%), upper respiratory tract infection (3%), injection site reaction (3%), fatigue (2%), back pain (3%), urinary tract infection (2%), abdominal pain (2%), migraine (2%), influenza-like illness (2%), neck pain (3%) and pyrexia (2%).
- 6.46 The submission presented the results of indirect comparisons of selected safety outcomes for Study 30068 versus PREEMPT1/2), Study 295 and REGAIN. The submission noted the following in relation to the indirect comparisons:
- Compared to Botox in the full trial population, there was a statistically significant difference in treatment-related adverse events for fremanezumab 225 mg 4-weekly and 675 mg 12-weekly (favouring fremanezumab), and a statistically significant difference in treatment-emergent adverse events for fremanezumab 225 mg 4-weekly (favouring fremanezumab). Adverse event data for PREEMPT1/2 for the subgroup of patient treatments was not available. The results of the indirect comparisons should be interpreted with caution due to the differences in the adverse event reporting periods between the trials (12 weeks in Study 30068 and 24 weeks in PREEMPT1/2).
 - Compared to erenumab in the full trial population, there were no statistically significant differences for fremanezumab 225 mg 4-weekly or 675 mg 12-weekly compared to erenumab 70 mg or 140 mg. In the subgroup of patients with ≥ 3 prior treatment failures, there was a statistically significant difference in treatment-emergent adverse events for fremanezumab 225 mg 4-weekly compared to erenumab 140mg (favouring fremanezumab).
 - Compared to galcanezumab in the full trial population, there were no statistically significant differences for fremanezumab 225 mg 4-weekly or 675 mg 12-weekly compared to galcanezumab 120 mg. Adverse event data for REGAIN for the subgroup of patients with ≥ 3 prior treatment failures was not available.

Benefits and harms

- 6.47 On the basis of the direct evidence presented in the submission, for the subgroup of patients with ≥ 3 prior treatment failures:

- for every 100 patients treated with fremanezumab 225 mg 4-weekly or fremanezumab 675 mg 12-weekly in comparison to placebo, approximately [REDACTED] - [REDACTED] more patients would have a $\geq 50\%$ reduction in monthly migraine days over 12 weeks.
 - patients treated with fremanezumab 225 mg 4-weekly or 675 mg 12-weekly would experience, on average, approximately [REDACTED] fewer migraine days per month than patients treated with placebo (reduction of 4 with fremanezumab, reduction of [REDACTED] with placebo) over 12 weeks of treatment
- 6.48 On the basis of the indirect evidence presented for patients with chronic migraine and the subgroup of patients with ≥ 3 prior treatment failures, patients treated with fremanezumab 225 mg 4-weekly or fremanezumab 675 mg 12-weekly would experience a similar reduction in migraine days per month compared to Botox, erenumab and galcanezumab and similar rates of adverse events.

Interpretation of clinical evidence

- 6.49 The submission described fremanezumab 225 mg 4-weekly and fremanezumab 675 mg 12-weekly as superior in terms of effectiveness, and non-inferior in terms of safety to placebo for the treatment of chronic migraine in patients who have tried and failed or are intolerant to ≥ 3 prior prophylactic treatments.
- 6.50 The evaluation considered this claim was adequately supported.
- Compared to placebo in Study 30068, treatment with fremanezumab 225 mg every 4 weeks and 675 mg every 12 weeks was associated with statistically significant improvements in monthly migraine days, monthly headache days, and the proportion of patients achieving a $\geq 50\%$ response in the full trial population and the subgroup of patients with ≥ 3 prior treatment failures.
 - However, the clinical claim relied on the results of post hoc subgroup analyses to define a cohort who would fulfil the requirements under the proposed restriction, and these analyses were considered to be at high risk of bias.
 - There was a lack of long-term comparative efficacy and safety data for fremanezumab, with the double-blind treatment period in Study 30068 limited to 12 weeks. The ESC noted the lack of long-term data was applicable to all CGRP inhibitors and considered that the clinical evidence presented in the submission supported the safety of fremanezumab for up to 15 months of treatment.
 - Treatment with fremanezumab 225 mg 4-weekly was associated with numerically greater reductions in monthly migraine days and headache days than the fremanezumab 675 mg 12-weekly arm. However, the fremanezumab 225 mg 4-weekly treatment regimen included a loading dose of 675 mg which resulted in a larger fremanezumab exposure over the 12 week trial period (1,125 mg vs 675 mg).

- 6.51 The PBAC considered the claim that fremanezumab is superior to placebo in terms of effectiveness was reasonable but the magnitude of the benefit was uncertain (use of a post hoc subgroup and inclusion of a loading dose in the 4-weekly treatment arm). The PBAC noted the provision of clinical data up to 15 months but considered the longer term benefit of fremanezumab remained uncertain. The PBAC considered the claim of non-inferior safety to placebo was not reasonable given the higher occurrence of injection site reactions but overall considered fremanezumab was reasonably well-tolerated.
- 6.52 The submission described fremanezumab 225 mg 4-weekly and fremanezumab 675 mg 12-weekly as non-inferior in terms of effectiveness and safety compared to Botox, galcanezumab and erenumab in the treatment of chronic migraine in patients with ≥ 3 prior treatment failures.
- 6.53 The evaluation considered this claim was not strongly supported.
- Indirect comparisons for the subgroup of patients with ≥ 3 prior treatment failures were at high risk of bias as they were conducted post hoc. The definitions used to specify the subgroup and the proportion of patients that met the definitions differed between the studies, suggesting that the identified subgroups of patients with ≥ 3 prior treatment failures may not be equivalent.
 - There were differences in trial design (outcome definition, concomitant medication allowed, time period for assessment of response) across the studies that may impact on transitivity.
 - There were differences in the placebo interventions between the trials (route of administration, number of injections, duration of administration, timing of the injections) which suggest that the placebo results may not be adequately similar for use as a common reference in an indirect comparison. Large differences in the results for the placebo arms between the studies suggest that an indirect comparison may not be appropriate.
 - The upper 95% confidence interval for several comparisons exceeded the nominated non-inferiority margin of 2 days for the change in monthly migraine days.
- 6.54 The PBAC noted a number of transitivity issues with the indirect comparisons but considered that, on balance, the claim of non-inferior comparative effectiveness and safety compared to Botox, galcanezumab and erenumab was uncertain but reasonably supported by the data.

Economic analysis

Cost utility analysis versus placebo

- 6.55 The submission presented a cost-effectiveness analysis and a cost-utility (CUA) analysis versus placebo (as a proxy for BSC) for patients who have either failed

treatment with Botox or are considered unsuitable for Botox treatment (Botox ruled out).

6.56 The key components of the economic evaluation are presented in Table 13.

Table 13: Key components of the economic evaluation

Component	Description	Comments
Type of analysis	Cost-effectiveness analysis and cost-utility analysis.	This was reasonable.
Options compared	Fremanezumab; placebo (as a proxy for BSC).	The placebo arm of Study 30068 may not be a suitable proxy for BSC. While patients in the trial were allowed to use acute medicines for the treatment of migraines, they were not permitted to use any prophylactic medications during the trial. This may not reflect the management of patients in the PBS population. The ESC considered this was unlikely to reflect the management of patients in clinical practice as patients treated with BSC or fremanezumab would receive additional treatment. The ESC further noted that patients may also receive subsequent treatment with Botox or other prophylactic treatments but this was not modelled and was likely to have a substantial impact on cost-effectiveness.
Outcomes	Quality-adjusted life years (QALYs)	This was reasonable.
Time horizon	5 years in the model base case versus 12 weeks double-blind treatment in Study 30068.	The submission presented data from an ongoing extension study of fremanezumab (Study 30051) to support the durability of treatment effect beyond 12 weeks.
Methods used to generate results	Markov microsimulation model.	The submission did not adequately justify the use of microsimulation to model the results of the comparison. The PSCR stated a micro-simulation was used to capture the migraine day distributions (i.e. the number of migraines per month), how these changed in each month of therapy, and the associated utilities and costs.
Health states	<ul style="list-style-type: none"> • On treatment - all patients • On treatment - responder • On treatment - non-responder • Off treatment • Death 	The choice of health states appeared reasonable. The 'on treatment - non-responder' health state was included in sensitivity analyses only.
Cycle length	4 weeks	This was reasonable.
Transition probability	Based on the pooled results for the 225 mg 4-weekly and 675 mg 12-weekly treatment arms in Study 30068 for the subgroup of patients with ≥ 3 prior treatments.	The inclusion of the 675 mg loading dose for the 225 mg 4-weekly arm included in the clinical trial may have resulted in overestimation of the treatment outcomes.
Utility values	Utility values mapped from the MSQ to EQ-5D-3L using an algorithm published by Gillard et al. (2012).	The submission did not present the results of EQ-5D-5L collected in the trial.
Software package	TreeAge Pro and Microsoft Excel	This was reasonable.

Source: Table 3.2, p.181 of the submission.

Abbreviations: MSQ, Migraine-Specific Quality of Life Questionnaire.

6.57 A summary of the key drivers of the economic model is presented in Table 14.

Table 14: Key drivers of the model

Description	Method/Value	Impact
Clinical evidence	The proportion of patients continuing treatment beyond 12 weeks in the model was based on the proportion of chronic migraine patients with ≥ 3 prior treatment failures in Study 30068 who achieved a $\geq 50\%$ reduction in monthly migraine days (█% in the fremanezumab arm; █% in the placebo arm). Fremanezumab response rates were based on the pooled results for the 225 mg 4-weekly and the 675 mg 12-weekly treatment arms. In the utilisation estimates presented in the submission, it was assumed that █% of patients will continue fremanezumab treatment beyond 12 weeks. This implies that a substantial number of patients are expected to remain on treatment beyond 12 weeks despite not having achieved the required reductions in monthly migraine days. The ESC noted that the model was sensitive to this parameter and even small changes increased the ICER significantly.	Moderate to likely high, favours fremanezumab
Discontinuations	The submission assumed a discontinuation rate of █% per year and stated that the rate applied in the model was based on discontinuations in Study 30051, adjusted to match the 4-week cycles of the model (█% per cycle). The source of the discontinuation rate was unclear and could not be validated during the evaluation. The assumed discontinuation rates were not considered to be reasonable, as they were likely to be higher than the continuation rates in clinical practice amongst patients who achieve a response ($\geq 50\%$ reduction in monthly migraine days). At the end of the 5 year model, only █% of fremanezumab patients remain on treatment.	Moderate, favours fremanezumab
Utilities	Utilities were based on MSQ data (baseline, Weeks 4 and 12) from Study 30068. The MSQ scores in Study 30068 (at baseline, and Weeks 4 and 12) were mapped to the EQ-5D-3L (UK set) using the chronic migraine 'simple' algorithm published by Gillard et al. (2012). The submission did not adequately justify the need for a complex mapping approach given that data for the EQ-5D-5L instrument were collected in the trial. Baseline results for the EQ-5D-5L questionnaire and results for the change from baseline were not presented in the submission. The ESC considered that the EQ-5D-5L results by responder status would have been informative and should have been provided with the submission. An 'on treatment' utility estimate was used for patients remaining on treatment in both the fremanezumab and placebo arms, and the 'off treatment' utility estimate was applied to all patients who had discontinued treatment. The ESC agreed with the evaluation that inclusion of a utility difference for being 'on treatment' versus 'off treatment' was not adequately justified. There is unlikely to be any difference in quality of life due to treatment status alone.	Moderate, favours fremanezumab
Monthly migraine days distributions	A beta binomial model was used to estimate the distribution of monthly migraine days around the mean monthly migraine days at baseline and during treatment. No models based on Study 30068 data were provided in the submission. Due to the structure of the model, it was not possible to test the impact of using alternative distribution models for monthly migraine days. The PSCR considered the distribution used addressed the PBAC's concern regarding implausible responder distributions observed in the erenumab economic model (erenumab, March 2019 PSD). The ESC considered the method for modelling the data was not well justified but noted the responder distributions appeared reasonable. The ESC considered it would have been informative to provide an analysis based on patient level data.	Unclear
Health resource use	Resource use (GP visits, Specialist visits, Nurse Practitioner visits, Emergency Department visits, hospitalisations, triptan use) by monthly migraine day categories was based on the distribution used in the UK erenumab submission to NICE, with adjustments applied for the Australian population. The ESC agreed with the evaluation that the complex, multi-step approach used in the submission to derive	Moderate, favours fremanezumab

Table 14: Key drivers of the model

Description	Method/Value	Impact
	resource utilisation estimates was difficult to interpret and included some inappropriate cost categories (e.g. nurse practitioner) for the Australian context.	
Extrapolation	The economic model assumed that patients who achieve a response ($\geq 50\%$ reduction in monthly migraine days from baseline) in the fremanezumab and placebo arms of the trial will maintain the response over the five years of the model. This assumption was uncertain given that lack of longer-term comparative effectiveness data for fremanezumab.	Likely high, favours fremanezumab

Source: Compiled using Section 3 of the submission.

Abbreviations: EQ-5D-3L, EuroQol 5-Dimension 3-Level; MSQ, Migraine-Specific Quality of Life Questionnaire.

6.58 Table 15 presents the results of the economic evaluation for fremanezumab versus BSC (placebo) for the base case.

Table 15: Results of the economic evaluation

	Fremanezumab	Placebo/BSC	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Migraine days	[REDACTED]	[REDACTED]	[REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per migraine day averted			\$ [REDACTED]
Incremental cost per QALY gained^a			\$ [REDACTED]

Source: Table 3.15, p.227 of the submission.

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.

^a The incremental cost per QALY reported in the submission differed slightly due to rounding of results in the submission.

6.59 The submission estimated that treatment with fremanezumab was associated with an incremental cost per QALY gained of \$ [REDACTED] compared to BSC.

6.60 Sensitivity analyses indicate that the model is most sensitive to changes in assumptions regarding the discontinuation rates for placebo, the probability of a response in the placebo arm, changes in the assumed utility values, and the proportion of patients continuing treatment without a response. The model appeared to be relatively insensitive to changes in the fremanezumab response rates, with costs and benefits changing proportionately over various tested response rates.

6.61 The PSCR noted that a sensitivity analysis was provided in the submission that assumed [REDACTED]% of non-responders continued on therapy and derived no clinical benefit but incurred additional drug costs, resulting in an ICER of \$45,000 - \$75,000 per QALY gained (compared to a base case of \$15,000 - \$45,000). The ESC noted that assuming [REDACTED]% of fremanezumab non-responders continued on therapy (consistent with the assumption in the financial estimates) and achieved partial responses of [REDACTED] to [REDACTED] days per month reduction resulted in ICERs between \$45,000 and \$75,000 (Table 16). The ESC noted that the economic model was sensitive to this assumption.

Table 16: Results of multivariate sensitivity analysis

	Incremental costs	Incremental QALYs	ICER
Base case: - Fremanezumab: █% responders; █% non-responders; █% partial responders. - Placebo/ BSC: 5% responders; 95% non-responders; 0% partial responders.	\$ █	█	\$ █
- Fremanezumab: █% responders; █% non-responders; █% partial responders (total responders and partial responders = █%). - Placebo/ BSC: unchanged. <ul style="list-style-type: none"> o Partial response mean of 7 days/month reduction o Partial response mean of 5 days/month reduction o Partial response mean of 3 days/month reduction 	\$ \$ █	█	\$ \$ █

Abbreviations: BSC, best supportive care; ICER incremental cost effectiveness ratio; QALY, quality-adjusted life year.

All sensitivity analyses based on 1,000 trials using the random number generator Seed 3.

Source: compiled using 'Frem variable list (FINAL)' Excel workbook and 'Migraine (FINAL) – Final - Base Case' TreeAge file.

6.62 The PBAC noted a number of assumptions in the economic model favoured fremanezumab (paragraph 6.57) and there were uncertainties regarding the appropriate continuation rate and clinical benefit to use in the model which had a significant impact on the ICER (paragraph 6.61)

Cost minimisation analysis versus Botox

6.63 The submission presented a CMA versus Botox for the population of chronic migraine patients who are eligible for treatment with Botox and proposed the following equi-effective doses: 3 syringes of fremanezumab (675 mg) are equivalent to █ vials of Botox (█ Units).

6.64 The proposed equi-effective doses were based on the average number of Botox vials dispensed per service (█ vials), derived from PBS dispensing data for Botox between April 2018 and March 2019. The evaluation considered this was not appropriate and that equi-effective doses should be based on the doses in the clinical trials. The PSCR argued real world dosing should be used as that is what the PBS is paying for. The ESC disagreed with the PSCR and considered equi-effective doses should be based on the clinical trial evidence used to determine non-inferiority.

6.65 Table 17 presents the results of the CMA for fremanezumab versus Botox using the published price of Botox. The ESC recalled that galcanezumab was recommended for listing on the basis of a CMA with Botox (164U every 12 weeks) over 2 years of treatment (paragraph 7.6, galcanezumab PSD, July 2019 PBAC meeting). The PBAC noted a difference in the Botox administration cost compared to the galcanezumab CMA (Table 12, galcanezumab PSD, July 2019 PBAC meeting).

Table 17: Results of the cost-minimisation analysis for fremanezumab versus Botox (using the published Botox price)

	Fremanezumab	Botox 200U
Proposed equi-effective dose	█ syringes	█ vials
Treatment cost (Botox)		
Drug acquisition, at AEMP (\$337.49 ex-man x █ vials x 8)	–	\$ █
Administration cost (\$107.85 x 8)	–	\$ █
Drug and administration cost per 2 years	–	\$ █
Cost-minimisation (fremanezumab)		
Drug acquisition, at AEMP (24 syringes)	\$ █	–
Specialist consultations (\$75.05 x 2)	\$150.10	–
GP visits (\$38.20 x 3.5)	\$133.70	–
Cost-minimised AEMP per 225 mg syringe (\$ █/24)	\$ █	–

Source: Section 3.10, p.243 of the submission.

Abbreviations: AEMP, ex-manufacturer price; GP general practitioner; U, units

- 6.66 The calculation of the equi-effective doses for fremanezumab and erenumab was based on a 50:50 dose split for erenumab 70 mg and 140 mg. The submission proposed the following equi-effective doses: 2,700 mg fremanezumab = 1,369 mg erenumab.
- 6.67 The submission noted that treatment with galcanezumab requires an initial loading dose of 240 mg followed by 120 mg monthly, resulting in a total of thirteen 120 mg syringes over the first 12 months. The submission proposed the following equi-effective doses: 2,700 mg fremanezumab = 1,560 mg galcanezumab.
- 6.68 The ESC considered the equi-effective doses to be fremanezumab 225 mg every month or 675 mg every three months, erenumab 70 mg or 140 mg every four weeks and galcanezumab 240 mg initially followed by 120 mg once monthly.
- 6.69 The submission derived a weighted price for fremanezumab based on the results of the CUA versus BSC (Botox ruled out and Botox failed populations) and the CMA versus Botox (Botox eligible population).
- 6.70 The relative weighting between the populations was based on the estimated number of Botox eligible (█) and Botox ineligible (█) patients in the first year of listing. The ESC considered the methodology used to derive the Botox eligible and Botox ineligible populations were not reliable and highly uncertain.
- 6.71 The submission only considered patients who are currently (i.e. in Year 1 of fremanezumab listing) receiving treatment with Botox to be Botox-eligible patients. However, there are likely to be additional patients with access to a neurologist, with no contraindication to Botox, and who do not have a toxin or needle failure who have not elected treatment with Botox. These patients may also be considered eligible for Botox. The weighting was derived based on the numbers of eligible patients for each of the subpopulations in the first year of listing only. However, the relative proportions are likely to change over the first six years of listing. The submission did not adequately justify basing the weighted price on the number of eligible patients rather than the number of anticipated treated patients.

6.72 Table 18 presents the derivation of the weighted fremanezumab price (using the published price for Botox for the CMA price). The PBAC considered the submission had not adequately justified a higher cost for fremanezumab in the Botox ruled out and Botox failed population.

Table 18: Requested fremanezumab weighted price

	Requested price (AEMP)	Weighting	Price/syringe
Cost-minimisation versus Botox	\$ [REDACTED]	[REDACTED] %	-
Cost-effectiveness versus placebo/BSC	\$ [REDACTED]	[REDACTED] %	-
Weighted AEMP per 225 mg syringe	-	-	\$ [REDACTED]
DPMQ for 225 mg (1 x 225 mg syringe)	-	-	\$ [REDACTED]
DPMQ for 675 mg (3 x 225 mg syringe)	-	-	\$ [REDACTED]

Source: Table 3.1, p.180 of the submission.

Abbreviations: AEMP, approved ex-manufacturer price; BSC, best supportive care; DPMQ, dispensed price for maximum quantity.

6.73 Based on the assumed weightings of [REDACTED] % for the Botox eligible and [REDACTED] % for the Botox ineligible populations, the weighted DPMQ for fremanezumab 225 mg was \$ [REDACTED] and the weighted DPMQ for fremanezumab 675 mg (3 x 225 mg syringes) was \$ [REDACTED]. The ESC considered the weighted price for fremanezumab was highly dependent on the proportion of use between the two populations which was uncertain.

Drug cost/patient/year

6.74 Table 19 provides a summary of treatment costs for fremanezumab 225 mg monthly and fremanezumab 675 mg three monthly.

Table 19: Drug cost per patient for fremanezumab

	Study 30068	Economic model	Financial estimates
Fremanezumab 225 mg monthly			
Dose	675 mg loading dose followed by 225 mg 4-weekly	225 mg monthly (based on calendar months)	225 mg monthly (based on calendar months)
Fremanezumab drug cost	\$ [REDACTED] (proposed weighted DPMQ)	\$ [REDACTED] (proposed DPMQ for Botox ruled out and Botox failed patients)	\$ [REDACTED] (proposed weighted DPMQ)
Treatment duration	12 weeks	Ongoing for responders	Ongoing for responders
Cost/patient/year ^a	\$ [REDACTED] ^b	\$ [REDACTED]	\$ [REDACTED]
Fremanezumab 675 mg 3-monthly			
Dose	675 mg 12-weekly	Not included	675 mg 3-monthly (based on calendar months)
Fremanezumab drug cost	\$ [REDACTED] (proposed weighted DPMQ)	Not included	\$ [REDACTED] (proposed weighted DPMQ)
Treatment duration	12 weeks	Not included	Ongoing for responders
Cost/patient/year ^a	\$ [REDACTED]	Not included	\$ [REDACTED]

Abbreviations: DPMQ, dispensed price for maximum quantity

Source: Table 3.1, p.180; Table 3.7, p.209 of the submission.

^a [REDACTED]

^b Excluding cost of loading dose.

6.75 The annual cost of treatment for fremanezumab 225 mg in the economic model (\$ [REDACTED]) was based on the proposed DPMQ of \$ [REDACTED] in the Botox ruled out and

Botox failed populations. The PBAC noted the annual cost of treatment for fremanezumab 225 mg at the cost-minimised price (DPMQ \$ [REDACTED], using the published price of Botox) was \$ [REDACTED].² The PBAC considered the difference in treatment costs between the populations was not adequately justified in the submission.

- 6.76 The annual cost of treatment for fremanezumab 225 mg in the financial estimates (\$ [REDACTED]) was based on the proposed weighted DPMQ (\$ [REDACTED]) derived using the proportion of Botox-eligible and Botox-ineligible (Botox ruled out, Botox failed) patients.

Estimated PBS usage & financial implications

- 6.77 This submission was not considered by the DUSC. The submission used a combined market share/epidemiological approach to estimate the utilisation and financial impacts associated with the requested listing.
- 6.78 The total number of eligible patients was derived based on the following three subpopulations: Botox ruled out patients, Botox eligible patients and Botox failed patients.
- 6.79 The submission stated that patients in the Botox ruled out subpopulation would have a needle or toxin phobia, no access to a specialist trained in Botox administration, or a contraindication to Botox. The approach used in the submission was likely to capture all eligible patients, including patients currently treated with Botox and Botox failed patients, leading to double counting of patients in the utilisation estimates.
- 6.80 The submission assumed that Botox eligible patients were patients who are currently receiving treatment with Botox, or who would be treated during the first six years of listing in the absence of a fremanezumab listing. However, there are likely to be additional patients who are eligible for Botox who have not been treated. The submission did not adequately define the difference between Botox eligible and Botox ruled out patients. The ESC considered the methodology used to derive the eligible populations (Botox eligible, Botox ruled out, Botox failed) was not reliable and highly uncertain.
- 6.81 The submission assumed that [REDACTED]% of patients across each of the subpopulations would continue treatment beyond 12 weeks based on the continuation rate for Botox at 24 weeks reported in the 2017 DUSC Botox review. This continuation rate differed from the continuation rate of [REDACTED]% assumed in the economic model, which was based on the proportion of patients achieving at least a 50% reduction in monthly migraine days in the subgroup of patients with ≥3 prior treatment failures in Study 30068. This implies that a substantial number of patients who do not meet the response criteria specified in the proposed restriction are expected to use fremanezumab beyond 12 weeks.

² AEMP \$ [REDACTED] (Table 18). Monthly: DPMQ \$ [REDACTED], treatment cost per year = 12 x \$ [REDACTED].

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- 6.82 The submission assumed that an additional █% of patients treated with fremanezumab would discontinue treatment each year. Given the lack of alternative treatments, and the convenience of fremanezumab administration compared to Botox, the discontinuation rate in subsequent years may be lower than estimated. There is also potential for patients to reinstate treatment at a later time.
- 6.83 The submission noted that Botox is subject to a special pricing arrangement. The proposed price for fremanezumab incorporated a █% weighting based on the CMA of fremanezumab versus Botox, and therefore, the fremanezumab price will require recalculation using the effective price of Botox.

Table 20: Estimated net cost to the PBS/RPBS of listing fremanezumab

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated eligible population						
Initiating patients	█	█	█	█	█	█
Continuing patients	█	█	█	█	█	█
225 mg 4-weekly scripts						
Initiating scripts ^a	█	█	█	█	█	█
Continuing scripts ^b	█	█	█	█	█	█
675 mg 12-weekly scripts						
Initiating scripts ^c	█	█	█	█	█	█
Continuing scripts ^d	█	█	█	█	█	█
Initiating patients						
Net PBS/RPBS cost	█	█	█	█	█	█
Net PBS/RPBS cost inclusive of █	█	█	█	█	█	█
Continuing patients						
Net PBS/RPBS cost	█	█	█	█	█	█
Net cost to the PBS						
Cost offsets for substituted Botox (published price)	█	█	█	█	█	█
Cost offsets for substituted triptans	█	█	█	█	█	█
Overall net cost to PBS/RPBS						
Cost to MBS ^e	█	█	█	█	█	█
Overall net cost to Government	█	█	█	█	█	█

Source: Table 4.5, p.255; Table 4.11, p.259; Table 4.14, p.263; Table 4.20, p.268 of the submission; Excel workbook 'Fremanezumab – Section 4 (FINAL) – Base Case (9 July 2019)'.

^a Assumes █ scripts for initiating patients in the first year of treatment.

^b Assumes █ scripts per year in all years of treatment.

^c Assumes █ for initiating patients in the first year of treatment.

^d Assumes █ scripts per year in all years of treatment.

^e Corrected for error in submission. The PSCR acknowledged the submission incorrectly overestimated the offsets for of Botox administrations.

- 6.84 The estimated net cost to the Government was \$30 - \$60 million in Year 1, increasing to over \$100 million in Year 6, a total of more than \$100 million over the first six years of listing.
- 6.85 The estimated costs to Government were considered to be uncertain due to the following reasons:
- Unreliable methodology to identify eligible patients (paragraph 6.79 and paragraph 6.80).
 - The assumed uptake rates for fremanezumab are likely to be underestimated in the initial years of listing.
 - The proportion of patients continuing therapy beyond the 12-week assessment period is a significant area of uncertainty (paragraph 6.81 and paragraph 6.82).
 - The submission assumed 100% compliance with treatment which is unlikely to occur in clinical practice. Compliance with fremanezumab is likely to be higher than for Botox given differences in cost, convenience, and the broadening of prescribing to allow subsequent continuing treatment scripts for fremanezumab to be written by GPs.
 - The cost offsets for Botox were substantially overestimated, as the submission assumed that patients who switch to fremanezumab would have stayed on Botox treatment over all remaining years of the budget impact estimates (i.e. no patients discontinued Botox), and that all patients received four Botox administrations per year. The PSCR disagreed that the cost offsets for Botox were overestimated and that the estimates did not assume that all patients initiated to Botox would have continued on Botox. The ESC noted that in Year 6, there were [REDACTED] Botox eligible patients treated with fremanezumab (either initiating or continuing from the previous year) and [REDACTED] Botox patients included as a cost offset.
 - The assumed reductions in triptan use and health professional visits may not be realised in clinical practice, as the assumed reductions in migraine days were based on responders in Study 30068.
- 6.86 The ESC considered the financial estimates to be very high and uncertain. The ESC noted the estimates were highly dependent on assumptions that were not well justified in the submission.

Quality use of medicines

- 6.87 The submission stated that the launch of fremanezumab will be underpinned by comprehensive training of health care professionals and patients on injection procedures, expected side-effects, and relevant tools to assist patients and health care professionals to assess migraine and headache days.
- 6.88 The submission stated that patients will be provided with starter kits including a patient education booklet and a headache diary. The submission stated that patients

will be provided with multiple options to receive instructions on injection procedures, including video or face-to-face injection training by registered nurses. Demonstration injection kits along with training material will be provided to clinics for neurologists and nurses to assist with patient training. Ongoing education will be provided to health care professionals involved in the treatment of patients with fremanezumab.

Financial management – risk sharing arrangements

- 6.89 The Sponsor proposed a risk-sharing arrangement, consisting of a [REDACTED] % rebate for PBS spending above specified annual caps. The ESC considered that the proposed rebate did not adequately share the risk of use above the proposed expenditure cap.
- 6.90 Table 21 presents the annual expenditure caps associated with the proposed risk-sharing arrangement.

Table 21: Proposed annual PBS expenditure caps for fremanezumab

	2020	2021	2022	2023	2024
Proposed PBS expenditure cap	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Proposed rebate for expenditure above cap	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %

Source: Table 4.22, p.273 of the submission.

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

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation for fremanezumab for the treatment of chronic migraine in patients who have experienced an inadequate response, intolerance or a contraindication to at least three prophylactic migraine medications. The PBAC considered fremanezumab was an alternative treatment to Botox and galcanezumab for patients with chronic migraine and provided a similar reduction in monthly migraine days. The PBAC was of a mind to recommend fremanezumab for listing on the basis of cost-minimisation to Botox or galcanezumab but deferred making a recommendation to address the uncertainties regarding the number of patients who would be treated and the net financial cost of listing fremanezumab on the PBS.
- 7.2 The PBAC considered there is a high clinical need for new migraine treatments and noted the large number of consumer comments received.
- 7.3 The PBAC noted the submission positioned fremanezumab as a treatment option for three groups of patients: those who are eligible to be treated with Botox but are either unwilling due to a needle or Botox phobia, or who are unable to access treatment from a Botox-accredited neurologist (“Botox ruled out” subpopulation); those who are eligible and willing to be treated with Botox (“Botox eligible” subpopulation) and those who have tried and failed or are intolerant to Botox (“Botox failed” subpopulation). The PBAC considered the methodology used to derive the three eligible populations

was arbitrary and highly uncertain. The PBAC considered the Botox ruled out and Botox eligible population were not well defined and there was likely to be overlap in the populations and double counting of patients.

- 7.4 The PBAC noted that the submission nominated Botox (■■■% of use based on the proportion estimated to be 'Botox eligible') and BSC (■■■% based on the proportion estimated to be 'Botox ruled out' or 'Botox failed') as comparators. The PBAC considered that although a proportion of patients eligible for fremanezumab may not currently be treated with Botox that this had been substantially overestimated in the submission. The PBAC recalled when considering galcanezumab in July 2019 that Botox was accepted as the appropriate main comparator, and this was consistent with galcanezumab being restricted to the same high need patient population as for Botox (paragraph 7.4, galcanezumab PSD, July 2019 PBAC meeting). The PBAC considered fremanezumab should also be restricted to this same high need patient population and advised that the main comparator for fremanezumab should be Botox. The PBAC also considered galcanezumab was an appropriate comparator as it was recommended at the July 2019 PBAC meeting.
- 7.5 The PBAC noted the clinical evidence presented in the submission was based on the results of Study 30068, a randomised controlled trial of fremanezumab versus placebo in patients with episodic (n=329) and chronic migraine (n=509). The PBAC noted the clinical claim in the submission was based on a post hoc subgroup of patients with ≥ 3 prior treatment failures to more closely reflect the intended PBS population. The PBAC considered that treatment with fremanezumab resulted in a clinically significant reduction of 3 to 4 migraine days per month (from a baseline of approximately 17) compared to placebo although there was uncertainty regarding the magnitude of the benefit (paragraph 6.51). The PBAC considered the claim of non-inferior safety to placebo was not reasonable given the higher occurrence of injection site reactions in the fremanezumab treatment arms but overall, considered fremanezumab was reasonably well-tolerated.
- 7.6 The PBAC noted the submission presented indirect comparisons of fremanezumab versus Botox and galcanezumab, based on all patients with chronic migraine and the subgroup of patients with ≥ 3 prior treatment failures. The PBAC noted there was no statistically significant difference in the mean change from baseline in the number of monthly migraine days between fremanezumab and Botox in the subgroup of patients with ≥ 3 prior treatment failures [■■■ (95%CI: ■■■, ■■■) for 4 weekly dose, ■■■ (95%CI: ■■■, ■■■) for 12 weekly dose], although the non-inferiority margin was not met for the 12 weekly dose (upper 95% CI exceeded 2). The PBAC noted there was no statistically significant difference for the mean change from baseline in number of monthly migraine days between fremanezumab and galcanezumab in the subgroup of patients with ≥ 3 prior treatment failures [■■■ (95%CI: ■■■, ■■■) for 4 weekly dose, ■■■ (95%CI: ■■■, ■■■) for 12 weekly dose], although the non-inferiority margin was not met (upper 95% CI exceeded 2). However, the PBAC noted there were statistically significant differences between fremanezumab 4 weekly and

galcanezumab (favouring fremanezumab) for the indirect comparison of this outcome in all patients with chronic migraine [■■■■(95%CI: ■■■■, ■■■■)]. The PBAC noted an indirect comparison of safety data for all patients with chronic migraine was presented in the submission (paragraph 6.46). The PBAC noted there were a number of transitivity issues with the indirect comparisons of fremanezumab versus Botox and galcanezumab (paragraph 6.53), but considered that on balance, the claim of non-inferior effectiveness and safety was supported. The PBAC considered that fremanezumab, Botox and galcanezumab all provided a similar reduction in monthly migraine days with comparable safety.

- 7.7 The PBAC considered were fremanezumab recommended for listing, it should be listed on a cost-minimisation basis versus Botox. The PBAC noted the equi-effective doses proposed in the submission were derived from PBS data. The PBAC considered the equi-effective doses should be sourced from the clinical data used to demonstrate non-inferiority (paragraph 6.64). The PBAC recalled the trial-based equi-effective dose in the galcanezumab submission was 164U of Botox (paragraph 6.40, galcanezumab PSD, July 2019 PBAC meeting) and given the same evidence base (PREEMPT 1 and 2) was used in the fremanezumab submission, considered it was appropriate to apply the same equi-effective dose to fremanezumab. On this basis the equi-effective doses are: fremanezumab 225 mg every month or 675 mg every three months and 164U of Botox every 12 weeks. The PBAC advised the CMA should be conducted over 2 years of treatment for both medicines
- 7.8 The PBAC noted that galcanezumab was also a relevant comparator and considered the equi-effective doses to be fremanezumab 225 mg every month or 675 mg every three months and galcanezumab 240 mg initially followed by 120 mg once monthly. The PBAC advised the CMA should be conducted over 2 years of treatment for both medicines.
- 7.9 The PBAC considered there was a high level of uncertainty regarding the number of patients who would be treated and the net financial cost of listing fremanezumab on the PBS. The PBAC noted the submission estimated 10,000 – 50,000 patients would be treated with fremanezumab in the first year, increasing to 10,000 – 50,000 in year 6 and considered these estimates were highly uncertain because the methodology used was not reliable. The PBAC noted the financial estimates included an offset for up to 10,000 – 50,000 Botox patients and considered this was based on assumptions that were not reasonable (paragraph 6.85). The PBAC considered there was a high risk of use outside the restriction criteria (paragraph 2.3) which further increased the uncertainty associated with the net financial cost. The PBAC agreed with the ESC that the proposed ■■■% rebate did not adequately share the risk of use above the proposed expenditure cap (paragraph 6.89).
- 7.10 The PBAC considered that a RSA with significant rebates above the caps will be required to manage the total financial impact of listing fremanezumab, noting highly uncertain and high financial estimates. The PBAC further considered that any RSA would likely need to take into account the use of Botox and be shared across any other

novel agents for this condition, such as other CGRP ligand antagonists, or CGRP receptor antagonists that might be listed on the PBS in the future.

7.11 The PBAC considered any resubmission for fremanezumab could be a minor submission and should provide the following:

- A revised restriction criteria with initial treatment prescribed by neurologists with continuing treatment prescribed by, or in conjunction with, a neurologist consistent with that recommended for galcanezumab (paragraph 8.1, galcanezumab PSD, July 2019 PBAC meeting).
- A revised CMA versus Botox over a 2 year time period using equi-effective doses of fremanezumab 225 mg every month or 675 mg every three months and 164U of Botox every 12 weeks.
- A revised estimate of patient numbers addressing the issues raised in paragraph 7.9.
- A revised estimate of the net financial cost of listing fremanezumab that addresses the proportion of patients continuing therapy beyond the 12 week assessment period and appropriately accounts for substitution with Botox (paragraph 6.85).
- Details regarding a risk share arrangement that appropriately manages the uncertainty regarding the size of the patient population and the risks identified in paragraph 2.3.

Outcome:

Deferred

8 Context for Decision

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

9 Sponsor's Comment

The Sponsor thanks the PBAC for its deliberations and will continue to work with the committee and the Department to make Fremanezumab available for Australian patients suffering with chronic migraine.