

## 6.12 FREMANEZUMAB

### **Injection 225 mg in 1.5 mL pre-filled syringe, Ajovy<sup>®</sup>, Teva Pharma Australia Pty Ltd**

#### **1 Purpose of Submission**

- 1.1 The Category 4 submission requested a new listing of fremanezumab 225 mg pre-filled syringe (PFS) to provide a quarterly dosing regimen, in addition to the existing PBS-listed fremanezumab 225 mg PFS monthly dosing regimen, for the continuing treatment of chronic migraine (CM).

#### **2 Background**

##### ***Registration status***

- 2.1 Fremanezumab PFS was registered on the Australian Register of Therapeutic Goods (ARTG) on 2 September 2019 for the ‘preventative treatment of migraine in adults’. The recommended dose is 225 mg monthly or 675 mg every 3 months (quarterly) by subcutaneous injection.

##### ***Previous PBAC consideration***

- 2.2 In November 2019, the Pharmaceutical Benefits Advisory Committee (PBAC) considered the initial submission for fremanezumab PFS quarterly and fremanezumab PFS monthly. The submission nominated Botox<sup>®</sup> and BSC as comparators. 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 3 months and galcanezumab 240 mg initially followed by 120 mg once monthly. The PBAC advised the cost minimisation analysis (CMA) should be conducted over 2 years of treatment for both medicines. The PBAC 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 Pharmaceutical Benefits Scheme (PBS).
- 2.3 In its March 2020 resubmission, the sponsor only requested listing the monthly dosing regimen. The PBAC recommended listing fremanezumab 225 mg PFS with the monthly dosing regimen in March 2020. Fremanezumab was first listed on the Pharmaceutical Benefits Scheme (PBS) on 1 August 2021.

### 3 Requested listing

3.1 The requested listing is shown in the table below. The submission requested the proposed changes be flown on to the autoinjector (AI) form of fremanezumab 225 mg to enable quarterly dosing for the AI form, if recommended.

Add new medicinal product pack as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Qty Packs	Max qty units	No. of Rpts	Available brands
FREMANEZUMAB					
fremanezumab 225 mg/1.5 mL injection, 1.5 mL syringe	NEW	3	3	1	Ajovy
Create new prescribing rule with new Restriction Summary / Treatment of Concept: [NEW 1]					
<b>Concept ID</b>	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction Type –</b> <input checked="" type="checkbox"/> Authority Required: Streamlined [New 1]				
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.				
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.				
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.				
	<b>Indication:</b> Chronic migraine				
	<b>Treatment Phase:</b> Continuing treatment				
	<b>Treatment criteria:</b> Must be treated by a specialist neurologist or in consultation with a specialist neurologist				
	<b>AND</b>				
	<b>Treatment criteria:</b> Patient must not be undergoing concurrent treatment with the following PBS benefits: (i) botulinum toxin type A listed for this PBS indication, (ii) another drug in the same pharmacological class as this drug listed for this PBS indication				
	<b>AND</b>				
	<b>Clinical criteria:</b> Patient must have previously received PBS-subsidised treatment with this drug for this condition,				
	<b>AND</b>				
	<b>Clinical criteria:</b> Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine days per month,				
	<b>AND</b>				
	<b>Clinical criteria:</b>				

	Patient must be appropriately managed by his or her practitioner for medication overuse headache, prior to initiation of treatment with this drug,
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must continue to be appropriately managed for medication overuse headache.
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be administered on a 3 monthly dosing schedule
	<b>Prescribing instructions:</b>
	Patient must have the number of migraine days per month documented in their medical records.

- 3.2 The requested maximum quantity (3 x 225 mg) and number of repeats (1 repeat) will provide 6 months of treatment to patients who require quarterly dosing. To be eligible for this quarterly dosing, patients are required to have received PBS-subsidised fremanezumab under this condition. This means that existing patients would be able to transition to quarterly dosing if required.

*For more detail on PBAC's view, see section 6PBAC outcome.*

## 4 Comparator

- 4.1 The submission nominated fremanezumab 225 mg administered monthly for 3 months as the comparator for fremanezumab 675 mg (as three concurrent 225 mg doses) administered quarterly. This is appropriate.

*For more details on PBAC's view, see section 6 PBAC outcome.*

## 5 Consideration of the evidence

### ***Sponsor hearing***

- 5.1 There was no hearing for this item.

### ***Consumer comments***

- 5.2 The PBAC noted and welcomed the input from an individual (1) and an organisation (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment which patients are currently experiencing with fremanezumab monthly PFS, including the reduction in the number of days migraine-free. Individuals also mentioned that listing the quarterly injection will improve quality of life due to less frequent injections.
- 5.3 The PBAC noted the comments from Migraine Australia indicating its full support of the quarterly dosing for the continuing treatment of chronic migraine to limit the risk of adverse effects or wastage, and that private patients who are already on the quarterly dosing should have access to the PBS-subsidised quarterly dosing without

the need to be put on the initial treatment phase. The PBAC noted that the submission's request was only for continuing patients who have responded to fremanezumab monthly and that the number of affected patients was unknown.

### Clinical trials

5.4 The submission presented the following clinical study reports.

5.5 As a Category 4 submission, no evaluation of the clinical evidence was undertaken.

**Table 1. Master list of direct trials and associated reports**

Study ID	Brief Description and list of associated reports	Description
<b>30068 (FOCUS)</b>	<b>Clinical Study Report:</b> Teva Branded Pharmaceutical Products R&D Inc. "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 (TV48125-CNS-30068 and 2017-002441-30)." In. ClinTrials. (TEVA)	Registration study Key RCT presented in Nov 2019 submission. Has monthly vs. quarterly vs. placebo dosing arms. Chronic migraine patients in PBS population subgroup evaluated.
<b>Blaiss 2019</b>	Blaiss CA, et al. (2019). Quarterly Administration of Fremanezumab Does Not Show "Wearing Off" Effect During Third Month After Injection: P155. 61st Annual Scientific Meeting American Headache Society. Philadelphia, PA. (Blaiss CA, Stevanovic D et al. 2019)	Investigates if quarterly dosing 'wears off' during month 3 (i.e., month prior to next quarterly dose).
<b>Cowan 2019</b>	<b>Conference poster:</b> Cowan RP, Ghandi SK, Cloud B, Cohen JM, Bruce DC, Ramirez-Campos V, Ahn AH, and Lipton RB. 2019. "Patient Preference for Dosing Regimen and Perception of Dosing Flexibility With Fremanezumab for Migraine: Results From a Patient Survey Following Completion of a 1-year Extension Study (IHC-PO-403)." In International Headache Congress (IHC). Dublin Ireland (Cowan RP, Ghandi SK et al. 2019b).	

Source: Ajovy quarterly main body of submission p13 and p14

PBS: Pharmaceutical Benefits Scheme, RCT: randomised controlled trial

### Clinical claim

5.6 The submission claimed non-inferior comparative effectiveness and non-inferior comparative safety of fremanezumab quarterly dosing compared with fremanezumab monthly dosing for the treatment of CM.

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

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

### Economic analysis

5.9 The submission presented a CMA of fremanezumab quarterly dosing compared with fremanezumab monthly dosing. The estimated equi-effective dose was 225 mg of fremanezumab monthly over 3 months is equal to 675 mg of fremanezumab quarterly.

- 5.10 The submission proposed that the published (\$488.89) and effective approved ex-manufacturer price (AEMP) (\$) remain unchanged. This is appropriate.
- 5.11 As a Category 4 submission, the economic analysis has not been independently evaluated.

***Estimated PBS utilisation and financial implications***

- 5.12 The submission used a market share approach to estimate the financial impact of listing fremanezumab quarterly. The submission suggested the requested listing is only expected to displace the current fremanezumab listing (for continuing patients) on a 1:3 basis (in terms of script volume) with no expected growth of the total market for fremanezumab. The submission claimed that uncertainty relating to the proposed listing of the quarterly dosing for fremanezumab (for continuation) is extremely low given that the limitations imposed by the cost-minimised price (vs. Botox and galcanezumab), the Risk Share caps, and the lack of incremental growth anticipated for the drug from the proposed listing. However, it is unclear whether patients would choose to start treatment with fremanezumab instead of galcanezumab because of the different dosing frequency. The pre-PBAC response noted that if this were to occur it would be cost neutral (at AEMP level) given that the anti-CGRPs are cost-minimised to each other and the impact of the shared Risk Share caps. The Sponsor did not expect an overall increase in the use of fremanezumab, rather that a modest proportion of patients will have a preference for less frequent dosing.
- 5.13 The proportion of fremanezumab monthly dosing sales displaced by the quarterly dosing (in continuation scripts) due to switching was derived from TEVA Australia internal uptake estimates and reflects the United States experience where 1% of all fremanezumab use was via the quarterly dose in June 2021 (fremanezumab was launched in the US in September 2018). This may not accurately reflect the market dynamics in Australia.
- 5.14 Table 2 presents the estimated extent of use, cost of fremanezumab quarterly to the PBS/RPBS and the net financial implications to the PBS/RPBS.
- 5.15 The submission estimated that 30,000 to <40,000 patients would be supplied fremanezumab quarterly over the first six years of listing at a net cost saving in Year 1 to Year 6 using the published price, and a cost of \$0 to < \$10 million in Year 1 to \$0 to < \$10 million in Year 6 using the effective price. These estimates are uncertain.
- 5.16 The co-payments required for a quarterly dosing regimen will be a third of the co-payments required for a monthly dosing regimen. This difference contributes to the estimated cost of the listing.
- 5.17 As a Category 4 submission, the financial estimates have not been independently evaluated.

**Table 2: Estimated use and financial implications to the PBS/RPBS**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed	<sup>1</sup>	<sup>2</sup>	<sup>2</sup>	<sup>3</sup>	<sup>4</sup>	<sup>5</sup>
<b>Net financial implications of fremanezumab (quarterly dosing) Published Price</b>						
Net cost to PBS/RPBS (-\$)	<sup>6</sup>	<sup>6</sup>	<sup>6</sup>	<sup>6</sup>	<sup>6</sup>	<sup>6</sup>
<b>Net financial implications of fremanezumab (quarterly dosing) Effective Price</b>						
Net cost to PBS/RPBS (\$)	<sup>6</sup>	<sup>6</sup>	<sup>6</sup>	<sup>6</sup>	<sup>6</sup>	<sup>6</sup>

Abbreviations: PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

Source: Table 4.13 and Table 4.14, p47-48 of the submission.

The redacted values correspond to the following ranges:

<sup>1</sup>30,000 to < 40,000

<sup>2</sup>50,000 to < 60,000

<sup>3</sup>70,000 to < 80,000

<sup>4</sup>80,000 to < 90,000

<sup>5</sup>90,000 to < 100,000

<sup>6</sup>0 to < \$10 million

For more detail on PBAC's view, see section 6 PBAC outcome.

## 6 PBAC Outcome

- 6.1 The PBAC recommended amending the existing listing of fremanezumab (Ajovy®) for the continuing treatment of chronic migraine to provide patients with options of both monthly dosing and quarterly dosing by:
- Increasing the maximum quantity from 1 to 3.
  - Reducing the number of repeats from 5 to 1.
- 6.2 The PBAC noted the equi-effective doses are 225 mg of fremanezumab monthly over 3 months = 675 mg of fremanezumab quarterly.
- 6.3 The PBAC noted it had considered and recommended the listing of an auto-injector (AI) form for fremanezumab at the same meeting. The PBAC recommended these restriction changes be flowed-on to the auto-injector form (AI) of fremanezumab.
- 6.4 The PBAC considered the cost-minimisation analysis of fremanezumab quarterly dosing compared with fremanezumab monthly dosing to be acceptable.
- 6.5 The PBAC noted that the submission's financial estimates proposed a minor cost to the PBS/RPBS at the effective level. The PBAC considered that listing of fremanezumab quarterly regimen should not result in a net cost to Government.
- 6.6 The PBAC considered the Safety Net early supply rule should continue to apply to fremanezumab.
- 6.7 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because fremanezumab quarterly dosing is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over fremanezumab monthly dosing, or not expected to address a high and urgent

unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

- 6.8 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 7 Recommended listing

- 7.1 Amend the continuing treatment phase of the currently listed fremanezumab PFS (12603H) to be suitable for quarterly dosing by increasing the maximum quantity (units/packs) from 1 to 3 and decreasing the repeats from 5 to 1 as follows:

- 7.2 Flow-on this change to the continuing treatment phase of fremanezumab AI.

*Amend maximum quantity/maximum number of repeats:*

MEDICINAL PRODUCT Medicinal Product Pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
FREMANEZUMAB					
fremanezumab 225 mg/1.5 mL injection, 1.5 mL syringe	12603H	43	43	51	Ajovy
fremanezumab 225 mg/1.5 mL injection, 1.5 mL syringe	12611R	1	1	2	Ajovy
fremanezumab 225 mg/1.5 mL injection, 1.5 mL pen device	NEW	3	3	1	Ajovy
fremanezumab 225 mg/1.5 mL injection, 1.5 mL pen device	NEW	1	1	2	Ajovy
<b>Restriction Summary 12029 / ToC: 12029</b>					
Concept ID	<b>Category / Program:</b> GENERAL – General Schedule (Code GE)				
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners				
	<b>Restriction Type –</b> <input checked="" type="checkbox"/> Authority Required: Streamlined				
	<b>Administrative Advice:</b> No increase in the maximum quantity or number of units may be authorised.				
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.				
	<b>Administrative Advice:</b> Special Pricing Arrangements apply.				
	<b>Indication:</b> Chronic migraine				
	<b>Treatment Phase:</b> Continuing treatment				
	<b>Treatment criteria:</b>				
	Must be treated by a specialist neurologist or in consultation with a specialist neurologist				

	<b>AND</b>
	<b>Treatment criteria:</b>
	Patient must not be undergoing concurrent treatment with the following PBS benefits: (i) botulinum toxin type A listed for this PBS indication, (ii) another drug in the same pharmacological class as this drug listed for this PBS indication
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have previously received PBS-subsidised treatment with this drug for this condition,
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have achieved and maintained a 50% or greater reduction from baseline in the number of migraine days per month,
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must continue to be appropriately managed for medication overuse headache.
	<b>Prescribing instructions:</b>
	Patient must have the number of migraine days per month documented in their medical records.

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

## **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 had no comment.