

An addendum to this Public Summary Document (PSD) has been included at the end of the document.

5.25 PREGABALIN, Oral solution 20 mg per mL, 473 mL, Pregabalin-AFT®, AFT Pharmaceuticals (AU) Pty Ltd

1 Purpose of item

- 1.1 The Category 4 submission sought an Authority Required (STREAMLINED) listing for pregabalin 20 mg per mL oral liquid (herein referred to as Pregabalin-AFT®) under the same conditions as the currently PBS-listed pregabalin capsules for neuropathic pain.

2 Background

- 2.1 Pregabalin-AFT was TGA registered on 16 September 2020 for the treatment of neuropathic pain in adults and as adjunctive therapy in adults with partial seizures with or without secondary generalisation.
- 2.2 The PBAC has not previously considered a submission for pregabalin oral solution.
- 2.3 Pregabalin capsules are currently listed on the PBS under the General Schedule as an Authority Required (STREAMLINED) listing for neuropathic pain.

3 Requested listing

- 3.1 The submission requested that Pregabalin-AFT be listed under the same circumstances as pregabalin capsules (2348N, 2335X, 2355Y and 2363J).
- 3.2 The new medicinal product pack is shown in italics.

MEDICINAL PRODUCT Medicinal Product Pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
<i>PREGABALIN Pregabalin 20 mg/mL oral liquid, 473 mL</i>	New	1	1	5	Pregabalin-AFT

- 3.3 The dose range for pregabalin for neuropathic pain according to the Product Information, is 150 to 600 mg (7.5 to 30 mL) per day given in two divided doses. Each prescription will provide 63 days of treatment for a patient on a daily dose of 150 mg (7.5 mL) or 15 days of treatment for a patient on a daily dose of 600 mg (20 mL). The maximum quantity and number of repeats are appropriate.

4 Comparator

- 4.1 The submission nominated the currently listed pregabalin capsules as the main comparators. This was appropriate.

- 4.2 The submission noted that TGA considered Pregabalin-AFT to be bioequivalent to the currently listed brand of pregabalin capsules, LYRICA 25 mg, 75 mg, 150 mg and 300 mg.
- 4.3 The submission claimed that the new formulation allows flexibility and convenience for dose titration when required and provides an alternative for patients with difficulties swallowing pregabalin capsules.

5 Consideration of the evidence

Sponsor hearing

- 5.1 There was no hearing for this item.

Consumer comments

- 5.2 The PBAC noted that no consumer comments were received for this item.

Pricing consideration

- 5.3 The submission requested listing Pregabalin-AFT on a cost-minimisation basis to pregabalin capsules. The sponsor proposed an approved ex-manufacturer price (AEMP) of \$ [REDACTED] for Pregabalin-AFT. This is equivalent to \$ [REDACTED] per mg. The submission claimed that an AEMP of \$ [REDACTED] provides a lower cost per treatment compared to pregabalin 25 mg and 75 mg capsules which account for the majority of the script volume. A cost comparison of Pregabalin-AFT and the currently listed pregabalin capsules based on the average recommended dose of 150 mg twice daily is summarised below. The pre-PBAC Response stated the Sponsor was not able to propose a lower AEMP which would provide a lower cost per treatment compared to 150 mg and 300 mg capsules.

Table 1: Cost comparison across PBS Listed products

	Pack size	Price per pack (AEMP) (\$)	Price per mg (\$)	Price per 300 mg treatment (\$)	Treatment days per pack size based on 300 mg dose	PBS total scripts per year (2020)
Sponsor Product						
Pregabalin-AFT Oral Liquid, 20 mg/mL	473 mL	[REDACTED]	[REDACTED]	[REDACTED]	31.53	N/A
Comparative Product						
25 mg capsules	56 capsules	\$3.73	\$0.002664	\$0.80	4.67	906,431
75 mg capsules	56 capsules	\$8.25	\$0.001964	\$0.59	14.00	1,246,705
150 mg capsules	56 capsules	\$12.66	\$0.001507	\$0.45	28.00	784,908
300 mg capsules	56 capsules	\$18.88	\$0.001124	\$0.34	56.00	405,599

Source: Table 2, p4 of the submission.

Estimated PBS utilisation and financial implications

- 5.4 The submission used a market share approach to estimate the uptake and financial implications of Pregabalin-AFT. The submission stated that Pregabalin-AFT is not expected to increase market size or growth and that only a fraction of patients will switch from using capsules to oral liquid.
- 5.5 The submission predicted that Pregabalin-AFT will substitute for 1% of pregabalin capsules within the first year of listing, increasing to 5% by the sixth year.

5.6 The submission estimated that the net financial impact to the PBS/RPBS will be a net save of \$0 to < \$10 million in Year 6 of listing, with a total net save to the PBS/RPBS of \$0 to < \$10 million over the first 6 years of listing. As the proposed price for Pregabalin-AFT is only lower compared to 25 mg and 75 mg pregabalin capsules, the estimated net save is dependent on the substitution rate of 25 mg and 75 mg capsules versus 150 mg and 300 mg capsules. The pre-PBAC Response indicated that the substitution rate of 300 mg capsules was potentially lower than that in the financial estimates because these pack sizes are generally prescribed for patients requiring a higher dose of 600 mg per day. The pre-PBAC Response noted that a lower substitution rate of 300 mg capsules would result in more cost-savings to the PBS.

Table 2: Estimated use and financial implications

	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Estimated extent of use						
Number of Pregabalin-AFT Oral Liquid scripts dispensed ^a	█ ¹	█ ²	█ ³	█ ⁴	█ ⁵	█ ⁵
Drug costs to PBS						
Cost of Pregabalin-AFT Oral Liquid to PBS	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Less co-payments	- █ ⁶	- █ ⁶	- █ ⁶	- █ ⁶	- █ ⁶	- █ ⁶
Net cost to PBS	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Drug costs to RPBS						
Cost of Pregabalin-AFT Oral Liquid to RPBS	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Less co-payments	- █ ⁶	- █ ⁶	- █ ⁶	- █ ⁶	- █ ⁶	- █ ⁶
Net cost to RPBS	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Cost of affected PBS/RPBS listings						
Pregabalin 25 mg 2348N	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Pregabalin 75 mg 2335X	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Pregabalin 150 mg 2355Y	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Pregabalin 300 mg 2363J	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Less patient co-payments	- █ ⁶	- █ ⁶	- █ ⁶	- █ ⁶	- █ ⁶	- █ ⁶
Total	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Net financial implications						
Net cost to PBS/RPBS	- █ ⁶	- █ ⁶	- █ ⁶	- █ ⁶	- █ ⁶	- █ ⁶

^a Assuming 11.58 scripts per patient per year as estimated by the submission. The submission assumed that up to 5% of market share could be switched from pregabalin capsules to Pregabalin-AFT Oral Liquid.

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

Source: Table 3, p5 of the submission, Excel workbook 'Appendix 2 – UCM-Release-3Workbook-v108 for PREGABALIN-AFT OL.xlsx'

The redacted values correspond to the following ranges:

¹ 20,000 to < 30,000

² 40,000 to < 50,000

³ 60,000 to < 70,000

⁴ 80,000 to < 90,000

⁵ 100,000 to < 200,000

⁶ \$0 to < \$10 million

5.7 As a Category 4 submission, neither the economic analysis nor the financial estimates analysis have been independently evaluated.

6 PBAC Outcome

6.1 The PBAC deferred making a recommendation about the PBS-listing of pregabalin 20 mg per mL oral liquid (Pregabalin-AFT) for the treatment of neuropathic pain to allow for utilisation analysis of the currently listed immediate release pregabalin capsules and to further consider potential quality use of medicines issues with Pregabalin-AFT.

- 6.2 The PBAC was concerned about reports of potential misuse and diversion of pregabalin (and gabapentinoids more broadly) in Australia. The Committee therefore considered it was prudent to review the utilisation of pregabalin and consider any current evidence of misuse and diversion in Australia prior to forming a view as to whether additional forms of pregabalin should be recommended for listing on the PBS. The PBAC referred the matter of pregabalin use to the Drug Utilisation Sub-Committee (DUSC) for consideration at a future meeting.
- 6.3 The PBAC noted the submission's claim that an oral liquid formulation of pregabalin would provide flexibility for dose titration and an alternative presentation for patients with swallowing difficulties. The PBAC was uncertain of the clinical need for an oral liquid formulation of pregabalin, noting the contents of pregabalin capsules could be dispersed in water or food for people with swallowing difficulties. The PBAC considered that input from clinicians and consumers would assist in determining the clinical need for a liquid formulation of pregabalin.
- 6.4 The PBAC considered that there was a potential for market growth if Pregabalin-AFT was listed on the PBS as there may be patients not currently on pregabalin capsules who would utilise an oral liquid formulation.

Outcome:

Deferred

Addendum to the November 2021 PBAC PSD:

4.02 PREGABALIN, Oral solution 20 mg per mL, 473 mL, Pregabalin-AFT®, AFT Pharmaceuticals (AU) Pty Ltd

7 Background

- 7.1 At its November 2021 meeting, the PBAC deferred making a decision about listing pregabalin 20 mg per mL oral liquid (Pregabalin-AFT) to further consider potential quality use of medicines concerns with this requested listing.
- 7.2 The PBAC requested that the Drug Utilisation Sub-Committee (DUSC) undertake a utilisation analysis of the immediate release formulations of pregabalin listed on the PBS to inform its consideration of this listing request.

8 Current Situation

- 8.1 The report of the utilisation analysis of the immediate release formulations of pregabalin listed on the PBS (the Report) was considered by DUSC at its February 2022 meeting.
- 8.2 The key findings of the Report and considerations of DUSC include the following:
 - There was a substantial reduction in the number of patients first supplied pregabalin from around 259,083 patients in 2017 to 198,309 in 2020 which may indicate the impact of prescriber education programs.
 - Based on 2020 data, the most common strength dispensed was 75 mg (39%) followed by 25 mg (28%). The highest strength (300 mg) represented around 10% of all prescriptions supplied.
 - The average daily dose across all age groups for an initial PBS prescription (100.3 mg) was less than the recommended starting dose for pregabalin (150 mg). DUSC considered that the lower supplied doses probably reflected prescribers using the lowest possible effective dose to minimise side-effects. However, DUSC noted that 16% of Australian pregabalin patients were only supplied the lowest dose capsules and there was no titration in dosing, which could indicate off-label use.
 - There was a large number of prescriptions in 2021 prescribed by rheumatologists and psychiatrists (around 18,000 scripts and 14,000 scripts respectively), which may indicate some potential use outside the PBS restrictions for the treatment of fibromyalgia, anxiety and depression. The DUSC noted that an analysis of NPS MedicineWise pregabalin data showed

that the majority of pregabalin use was for lower back pain, which is outside the PBS indication¹.

- Reporting by the National Drug and Alcohol Research Centre notes the number of deaths involving pregabalin increased from less than 20 in 2015 to 100 in 2017 with most deaths resulting from a combined use with opioids. The DUSC considered this may indicated additive or synergistic effect.
- The DUSC noted that potentially harmful use of pregabalin is not uncommon, observed in approximately 13% to 15% of Australian pregabalin users².

8.3 The DUSC received comments and input on the Report from a number of stakeholders including the RACGP, drug sponsors and organisations (Australian Rheumatology Association, Pain Australia and Musculoskeletal Australia). The input from organisations indicated that pregabalin is being used to treat medical conditions other than neuropathic pain and some patients are receiving lower than the recommended dose. It was noted by the consumer organisations that while pregabalin can be of benefit for some, for others it is not, and the significant side effects can lead to individuals choosing to discontinue use. These side effects include drowsiness, dizziness, and dry mouth, weight gain, constipation, fatigue, brain fog/memory loss, irritability and hallucinations. It was noted by these organisations that many people are not aware of the potential side effects before taking pregabalin and more support and monitoring is needed for people who have been prescribed pregabalin

9 PBAC Outcome

- 9.1 The PBAC did not recommend the listing of pregabalin 20 mg per mL oral liquid (Pregabalin-AFT) for the treatment of neuropathic pain. The PBAC's decision was based on a lack of established clinical need for an oral liquid formulation of pregabalin and concerns about the quality use of medicines.
- 9.2 The PBAC recalled its view that the clinical need for an oral liquid formulation of pregabalin was uncertain, noting the contents of pregabalin capsules could be dispersed in water or food for people with swallowing difficulties. The PBAC considered that clinical need for an oral liquid formulation of pregabalin was not adequately established from the stakeholder input.
- 9.3 The PBAC noted from the Report that the larger number of pregabalin scripts prescribed by rheumatologists and psychiatrists may indicate use outside the PBS restrictions, though the PBAC noted the extent of use outside the restrictions could not be discerned from the PBS data. The PBAC noted that the input from organisations to the Report supported that pregabalin is being used outside of the PBS restrictions to treat medical conditions other than neuropathic pain.
- 9.4 The PBAC noted that the stakeholder input emphasised there were significant side effects associated with pregabalin, of which many patients were not aware.

¹ NPS MedicineWise 'Practice Review – Revising pregabalin: Optimising safety in prescribing for neuropathic pain. Accessed at: <https://www.nps.org.au/pbs-pregabalin>

² Cairns R, Schaffer AL, Ryan N, Pearson SA, Buckley NA. Rising pregabalin use and misuse in Australia: trends in utilization and intentional poisonings. *Addiction* 2019;114:1026–34.

- 9.5 The PBAC noted that while the Report indicated a substantial reduction in the number of patients first supplied pregabalin, the reduction in initiations for younger patients (aged up to 24 years) is less relative to older persons. The PBAC also noted that a high proportion (28%) of younger patients were identified as being supplied pregabalin with an opioid or benzodiazepine, mainly oxycodone, tramadol and diazepam. The PBAC considered that concomitant use of pregabalin with other drugs was a potential concern, noting that most toxicity for pregabalin is associated with its use with opioids, benzodiazepines, alcohol or illegal drugs. The PBAC considered that a particular concern is the mortality risk from drug interactions when pregabalin is co-administered with opioids and/or benzodiazepines, which can increase the risk of respiratory depression.
- 9.6 The PBAC considered that potential for increased misuse and overdosing with an oral liquid formulation of pregabalin could not be ruled out.
- 9.7 Overall, the PBAC considered there was inadequate rationale for listing an oral liquid formulation of pregabalin given the absence of established clinical need and in the context of the quality use of medicines concerns.
- 9.8 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not Recommended

10 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.

11 Sponsor's Comment

The sponsor had no comment.