

5.28 SIPONIMOD

Tablet 1 mg,

Mayzent[®],

Novartis Pharmaceuticals Australia Pty Limited

1 Purpose of Submission

- 1.1 The Category 4 submission requested a General Schedule Authority Required (STREAMLINED) listing of new form of siponimod (Tablet 1 mg) under the same conditions as the currently Pharmaceutical Benefits Scheme (PBS) listed forms of siponimod.

2 Background

- 2.1 Siponimod 0.25 mg (120 tablet and 12 tablet packs) and 2 mg tablets are currently listed on the PBS as Authority Required (STREAMLINED) listings for multiple sclerosis (MS).
- 2.2 Two pack sizes of siponimod 0.25 mg are listed on the PBS: a 12-tablet initiation pack and a 120-tablet pack for maintenance treatment.

Drug metabolism and Population

- 2.3 The submission stated that siponimod is eliminated from the systemic circulation by metabolism predominantly mediated through the polymorphic enzyme cytochrome P450 CYP2C9 and to a lower extent through CYP3A4.
- 2.4 The submission categorised the patient population for siponimod as poor metabolisers (patients with CYP2C9 *3*3 genotype which accounts for <1% of the population), intermediate metabolisers (patients with a CYP2C9 *2*3 or *1*3 genotype which accounts for approximately 12% of the population) and extensive metabolisers (accounts for approximately 88% of the population).

Registration status

- 2.5 Siponimod 1 mg tablet was TGA registered on 20 July 2023 for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS).
- 2.6 The TGA's evaluation of chemical and pharmaceutical data (ECPD) stated that siponimod 0.25 and 1 mg commercial tablets have the same qualitative composition and manufacturing process. It further stated that the 0.25 and 1 mg tablets differ in the drug load, the quantity of excipient lactose monohydrate used to compensate the drug load difference, and the slight difference in the iron oxide colorant components in the non-functional film-coating.
- 2.7 The TGA's ECPD did not establish direct bioequivalence between siponimod 1 mg and 0.25 or 2 mg tablets but accepted the sponsor's justification for not submitting

bioequivalence data for siponimod 1 mg tablets. This justification was made and accepted on the basis of the in vitro data provided, a comparison of the dissolution of siponimod 1 mg and 0.25 mg tablets.

- 2.8 The TGA approved Product Information (PI) states that the CYP2C9 genotype of the patient should be determined before initiation of siponimod.
- 2.9 According to the approved PI, the recommended maintenance dose of siponimod is 2 mg per day or 1 mg per day for patients with a CYP2C9*2*3 or *1*3 genotype. Siponimod is contraindicated in patients with CYP2C9*3/*3 genotype.

Previous PBAC consideration

- 2.10 Siponimod 1 mg tablet has not been considered by the PBAC previously.
- 2.11 At its July 2020 meeting, the PBAC recommended siponimod 0.25 and 2 mg forms for secondary progressive MS. At the time of this recommendation, the sponsor indicated that siponimod 1 mg was administered as 4 x 0.25 mg since it was not manufacturing the 1 mg tablet form. The submission indicated the sponsor intended to register a 1 mg form at a later date (Paragraph 3.9, Siponimod PSD, July 2020).

3 Requested listing

- 3.1 The submission requested the following new listing, identical to the existing listing of siponimod 0.25 mg (120 pack size). A shortened version of the requested listing is presented below and suggested additions are in italics.
- 3.2 The submission stated that the 1 mg maintenance dose of siponimod for patients determined to be poor metabolisers is currently administered as 4 x 0.25 mg tablets and that the proposed listing would reduce the tablet burden for these patients.

Public Summary Document – March 2024 PBAC Meeting

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
SIPONIMOD					
siponimod 250 microgram tablet, 12	12172P MP	1	12	0	Mayzent
siponimod 250 microgram tablet, 120	12160B MP	1	120	5	Mayzent
siponimod 2 mg tablet, 28	12158X MP	1	28	5	Mayzent
<i>siponimod 1 mg tablet, 28</i>	<i>NEW</i> <i>MP</i>	<i>1</i>	<i>28</i>	<i>5</i>	<i>Mayzent</i>
Restriction Summary: 10952 / Treatment of Concept: 10955					
Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code]				
	Indication: Multiple sclerosis				
	Treatment Phase: Initial treatment				
Restriction Summary 10953 / Treatment of Concept: 10953					
Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code]				
	Indication: Multiple sclerosis				
	Treatment Phase: Continuing treatment (including recommencement of treatment)				

4 Comparator

- 4.1 The submission nominated siponimod 4 x 0.25 mg as the comparator. The PBAC considered that this was appropriate.
- 4.2 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy.

For more detail 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 that no consumer comments were received for this item.

Clinical claim

5.3 The submission did not make a specific clinical claim. However, the PBAC considered that a claim of non-inferior comparative effectiveness and safety to siponimod 4 x 0.25 mg tablets was adequately supported.

Economic analysis

5.4 The submission presented a cost-minimisation analysis (CMA) of siponimod 1 mg tablet compared with siponimod 2 mg tablet (Table 1), claiming that the rationale was that the PBAC did not differentiate between the standard maintenance dose (siponimod 2 or 1 mg tablets) following its July 2020 recommendation of siponimod 2 mg tablet. The pre-PBAC response reiterated this claim and argued that it will be appropriate to cost minimised to the 2 mg siponimod tablet as there has been no determination of differing efficacy between 1 mg and 2 mg siponimod tablets. The PBAC noted that cost minimising to siponimod 2 mg tablet was inconsistent with the nominated clinical comparator, siponimod 0.25 mg form and considered that the 0.25 mg tablets (120 unit pack) was the appropriate comparator.

5.5 The submission did not provide an equi-effective dose for siponimod 1 mg, however, the submission stated that siponimod 1 mg was equivalent to siponimod 4 x 0.25 mg.

5.6 The submission requested the same effective ex-manufacturer price (EMP) and published approved EMP (AEMP) per pack for siponimod 1 mg tablet as the currently listed siponimod 2 mg tablet. The current effective EMP of the 2 mg form is three cents greater than the effective EMP of the 0.25 mg form (see Table 2 for details).

Table 1: Cost minimisation analysis based on effective price

	Current		Proposed
	Mayzent 2 mg	Mayzent 0.25 mg	Mayzent 1 mg
Cost per pack (effective EMP)	\$	\$	\$
Pack size	28	120	28
Days of treatment (tablets per pack/tablets per day)	28	30	28
Packs per year (365.25/days of treatment)	13.04	12.18	13.04
Cost per year (effective* EMP x packs per year)	\$	\$	\$

Source: Table 4, pp. 3 of the submission main body

*stated as 'published' in Table 4 of submission's main body - the cost-minimisation spreadsheet provided with submission confirmed it was incorrect)

Abbreviations: AEMP = approved ex-manufacturer price

5.7 As a Category 4 submission, the economic analysis has not been independently evaluated.

Estimated PBS usage and financial implications

5.8 The submission adopted a market share approach to estimate the net financial impact of listing siponimod 1 mg tablet. The submission assumed that siponimod 1 mg tablet

is expected to substitute for siponimod 4 x 0.25 mg tablet at a 100% substitution rate over a period of 6 years.

- 5.9 Table 2 and 3 present the estimated extent of use, cost of listing siponimod 1 mg tablet and the net financial implications to the PBS/RPBS at the effective and published AEMP of both the original cost model provided with the submission and the revised cost model. The financial impact to Services Australia will be determined by that agency as part of the post PBAC process.
- 5.10 The original cost model provided by the submission estimated that the proposed listing of siponimod 1 mg tablet will result in a financial impact of \$0 to < \$10 million (based on the effective price) or \$0 to < \$10 million (based on the published price) to the PBS/RPBS over a period of six years (Table 2).
- 5.11 In addition to the small difference in AEMP, the original cost model and submission considered that due to the difference in pack size between siponimod 1 mg and 0.25 mg tablets, there would be a financial impact from the listing of siponimod 1 mg tablet compared to siponimod 0.25 mg tablet based on the increased number of prescriptions required per year of treatment. The submission claimed that this increase in cost per year for siponimod 1 mg tablet should be considered as the removal of a discount to align the cost of therapy between both maintenance doses.
- 5.12 This cost model also estimated that there will be a total of 5,000 to < 10,000 scripts over the first six years of listing (500 to < 5,000 in Year 1 and 500 to < 5,000 in Year 6).
- 5.13 A revised cost model was requested due to the following:
- 14 months of scripts were incorrectly used as a year.
 - The last full calendar year (2023) of script volumes from the Services Australia website was not used.
 - The script equivalence of the proposed medicine and the existing medicine had been transposed.
 - The AEMP, maximum quantity and DPMQ for all published and effective prices were incorrect.
 - Outdated co-payment as each January the PBS co-payments are indexed in line with CPI.
- 5.14 The revised cost model provided estimated that there will be a total of 5,000 to < 10,000 scripts over the first six years of listing and claimed that the proposed listing of siponimod 1 mg tablet will result in a saving of \$0 to < \$10 million (based on the effective price) or \$0 to < \$10 million (based on the published price) to the PBS/RPBS over a period of six years (Table 3).
- 5.15 The PBAC considered that the proposed listing was likely to result in a minor cost to the PBS/RPBS due to the higher AEMP requested and the increased frequency of dispensing required compared to the existing 0.25 mg siponimod listing.

Public Summary Document – March 2024 PBAC Meeting

5.16 Both the original and revised cost models claimed that the proposed listing of siponimod 1 mg tablet will result in no financial impact to the RPBS due to there being no prescriptions currently dispensed under the RPBS. The PBAC noted that a financial impact to the RPBS would be expected if prescriptions are dispensed.

Table 2: Original estimated use and financial implications for siponimod 1 mg tablet.

Year	2024	2025	2026	2027	2028	2029
Estimated extent of use						
Total number of prescriptions	1	1	1	1	1	1
Estimated financial implications of siponimod 1 mg tablet (effective price)						
Cost to PBS (new listing)	2	2	2	2	2	2
Changed listing	3	3	3	3	3	3
Net cost to PBS	2	2	2	2	2	2
Cost to RPBS (new listing)	2	2	2	2	2	2
Changed listing	2	2	2	2	2	2
Net cost to RPBS	2	2	2	2	2	2
Total net cost to PBS/RPBS	2	2	2	2	2	2
Estimated financial implications of siponimod 1 mg tablet (published price)						
Cost to PBS (new listing)	2	2	2	2	2	2
Changed listing	3	3	3	3	3	3
Net cost to PBS	2	2	2	2	2	2
Cost to RPBS (new listing)	2	2	2	2	2	2
Changed listing	2	2	2	2	2	2
Net cost to RPBS	2	2	2	2	2	2
Total net cost to PBS/RPBS	2	2	2	2	2	2

Source: Table 5 and 6, pp. 3 of the submission main body; Tab 3a and 5 of the utilisation and financial estimate workbook provided with the submission.

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

The redacted values correspond to the following ranges

¹500 to < 5,000

²\$0 to < \$10 million

³net cost saving

Table 3: Revised estimated use and financial implications for siponimod 1 mg tablet.

Year	2024	2025	2026	2027	2028	2029
Estimated extent of use						
Total number of prescriptions	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated financial implications of siponimod 1 mg tablet (effective price)						
Cost to PBS (new listing)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Changed listing	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost to PBS	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Cost to RPBS (new listing)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Changed listing	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Net cost to RPBS	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Total net impact to PBS/RPBS	█ ³					
Estimated financial implications of siponimod 1 mg tablet (published price)						
Cost to PBS (new listing)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Changed listing	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost to PBS	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Cost to RPBS (new listing)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Changed listing	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Net cost to RPBS	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Total net impact to PBS/RPBS	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³

Source: Revised utilisation and financial estimate workbook.

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

The redacted values correspond to the following ranges

¹500 to < 5,000

²\$0 to < \$10 million

³net cost saving

5.17 As a Category 4 submission, the financial estimates have not been independently evaluated.

6 PBAC Outcome

6.1 The PBAC recommended the General Schedule, Authority Required (STREAMLINED) listing of siponimod, tablet 1 mg, under the same circumstances as the PBS-listed siponimod 0.25 mg tablets. This recommendation was made on a cost-minimisation basis to siponimod 0.25 mg tablet.

6.2 The PBAC advised that the cost-minimisation should be to the nominated clinical comparator, siponimod 0.25 mg tablet and that the price of tablet 1 mg should not be any higher than the 0.25 mg tablet on a per day basis.

6.3 The PBAC noted that the 1 mg tablet 28-unit pack size would provide 28 days of therapy, compared to the existing 0.25 mg tablet 120-unit pack size listing which provides 30 days of therapy. The PBAC considered that the listing of the 1 mg tablet should not result in an increased cost to Government.

6.4 The PBAC considered that although the submission did not directly make a clinical claim, it would be reasonable to claim non-inferior comparative effectiveness and safety to siponimod 4 x 0.25 mg tablet.

- 6.5 The PBAC recalled that the sponsor had indicated in its July 2020 submission that they intend to register a 1 mg siponimod tablet.
- 6.6 The PBAC considered that the equi-effective doses were 1 x 1 mg siponimod tablet once daily and 4 x 0.25 mg siponimod tablets per day.
- 6.7 The PBAC noted that the sponsor intends to replace the 120-tablet maintenance pack of 0.25 mg siponimod with siponimod 1 mg tablet on the PBS and would subsequently delist the 0.25 mg siponimod maintenance pack from the PBS. The PBAC also noted that the 12-tablet initiation pack of 0.25 mg siponimod would remain listed on the PBS.
- 6.8 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because siponimod 1 mg tablet is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over 4 x 0.25 mg siponimod tablets 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 2022* for Pricing Pathway A were not met.
- 6.9 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

- 7.1 Add new form of siponimod under the same conditions as the currently listed forms of siponimod as follows:

Public Summary Document – March 2024 PBAC Meeting

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
SIPONIMOD					
siponimod 1 mg tablet, 28	NEW MP	1	28	5	Mayzent
Restriction Summary: 10952 / Treatment of Concept: 10955					
Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code]				
	Indication: Multiple sclerosis				
	Treatment Phase: Initial treatment				
Restriction Summary 10953 / Treatment of Concept: 10953					
Concept ID (for internal Dept. use)	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code]				
	Indication: Multiple sclerosis				
	Treatment Phase: Continuing treatment (including recommencement of treatment)				

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.