

## **7.12 AMIFAMPRIDINE,**

**Tablet 10 mg,**

**Ruzurgi<sup>®</sup>,**

**The Trustee for Orspec Pharma Unit Trust**

### **1 Purpose**

- 1.1 The early re-entry resubmission sought to list amifampridine with an Authority Required listing (Telephone/Online) for amifampridine for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and children aged 6 years and above.
- 1.2 The resubmission incorporated the PBAC advice provided for the first amifampridine submission, which was considered at the November 2021 meeting.

### **2 Background**

- 2.1 Amifampridine was listed on the Australian Register of Therapeutic Goods (ARTG) on 14 September 2021 for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and children aged 6 years and above.
- 2.2 In November 2021, the PBAC considered there was a high clinical need for effective treatments for LEMS patients. The PBAC considered that a claim of superior efficacy of amifampridine compared to placebo was reasonable, albeit with an uncertain magnitude given the limitations of the available clinical evidence. The PBAC considered that the safety of amifampridine was inferior to placebo. The PBAC noted that a revised economic model was submitted with the pre-PBAC response that addressed some of the concerns raised in the evaluation and ESC advice. However, the PBAC considered the incremental cost effectiveness ratio (ICER) remained high and uncertain at the proposed price. The PBAC considered the approach used to estimate the proposed number of patients to be treated with amifampridine was reasonable (paragraphs 7.1, 7.8 to 7.11, amifampridine PBAC Public Summary Document (PSD), November 2021 PBAC meeting).

*For more detail on PBAC's view, see section 5 PBAC outcome.*

### **3 Requested listing**

- 3.1 The resubmission accepted the Secretariat suggestions for the requested listing provided for the first amifampridine submission considered in November 2021 (paragraph 3.1, amifampridine PSD, November 2021 PBAC meeting).
- 3.2 The proposed restriction presented in the resubmission is shown below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough. The Pre-PBAC response considered the proposed changes appropriate.

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
AMIFAMPRIDINE					
amifampridine 10 mg tablet, 100	NEW	2	200	5	Ruzurji
<b>Restriction Summary / Treatment of Concept: [New 1]</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 – (telephone/online PBS Authorities system)					
<b>Indication:</b> Lambert-Eaton myasthenic syndrome (LEMS)					
<b>Treatment Phase:</b> [blank]					
<b>Population criteria:</b>					
Patient must be each of: (i) untreated with this drug, (ii) diagnosed with the condition stated in the PBS indication; or					
Patient must be continuing PBS-subsidised treatment with this drug; or					
Patient must be transitioning from non-PBS supply to PBS-subsidised supply, involving one of: (i) treatment with this drug via the Therapeutic Goods Administration's Special Access Scheme (SAS) for this condition, (ii) a source other than the SAS for this condition; apply under this transitioning criterion once only;					
<b>Clinical criteria:</b>					
The condition must not be any of: (i) myasthenia gravis, (ii) Guillain-Barre syndrome					
<b>Treatment criteria:</b>					
Must be treated by a prescriber type identifying as at least one of the following: (i) a clinical immunologist, (ii) a neurologist, (iii) a medical practitioner working under the direct supervision of one of these mentioned specialists					
<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> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.					

3.3 The resubmission noted that patients are currently receiving amifampridine through the Special Access Scheme (SAS) and a company-sponsored compassionate use program. It would be reasonable to expect that these patients would want to access amifampridine via the proposed PBS listing as grandfathered patients. The resubmission proposed a single treatment phase listing for initial, continuing and grandfathered patients, consistent with the Secretariat suggestions provided for the first amifampridine submission considered in November 2021. For the resubmission, it was further suggested by the Secretariat to simplify the restriction by deleting the Population Criteria as shown above.

3.4 With regard to: (1) targeting subsidy to a correct diagnosis and (2) continuing treatment in a genuinely responsive patient, the resubmission suggested two differential diagnoses to be excluded (myasthenia gravis and Guillain-Barre syndrome)

and limiting prescribing to specialist prescribers rather than introducing potentially complex continuing rules. This was consistent with comments from the Secretariat on the restriction proposed for the November 2021 consideration.

- 3.5 The proposed restriction did not address treatment with amifampridine in relation to the presence or absence of malignancy, noting that paraneoplastic LEMS (pLEMS) is strongly associated with small cell lung cancer (SCLC), and that clinical symptoms of pLEMS usually precede the SCLC diagnosis. Patients with either pLEMS or autoimmune LEMS (aLEMS) will be eligible for amifampridine under the proposed listing.
- 3.6 The requested restriction specified a listing for 10 mg tablets in packs of 100, with a maximum quantity of 2 packs (i.e. 200 tablets/2,000 mg in total), and 5 repeats to allow for 6 months of treatment. The TGA approved Product Information for amifampridine states that dosing should be individualised based on clinical circumstances and patient response, and involves titrating to the optimal effective dose with minimum side effects. The maximum total maintenance dose is 100 mg per day. This would suggest that increases (i.e. the maximum quantity multiplier) of up to twice the listed maximum quantity should be permitted to be approved by Services Australia if sought. It is therefore suggested to delete the Administrative Advice stating that “No increase in the maximum quantity or number of units may be authorised”.

*For more detail on PBAC’s view, see section 5 PBAC outcome.*

## **4 Consideration of the evidence**

### ***Sponsor hearing***

- 4.1 There was no hearing for this item.

### ***Consumer comments***

- 4.2 The PBAC noted that no consumer comments were received for this item in relation to the resubmission. The PBAC previously noted and welcomed the input from individuals (9), a health care professional (HCP), and an organisation via the Consumer Comments facility on the PBS website in relation to consideration of amifampridine at the November 2021 PBAC meeting (paragraph 6.2, November 2021 PBAC PSD).

### ***Comparative effectiveness***

- 4.3 The November 2021 consideration of amifampridine was based on two small randomised, double-blind, placebo-controlled trials: DAPPER (published in 2018) and DUKE (published in 2000). The DAPPER trial included patients who were successfully taking amifampridine for at least three months, whilst the DUKE trial assessed patients who were treatment naïve to amifampridine. No additional clinical data were presented in the resubmission.

***Economic analysis***

- 4.4 As an early re-entry resubmission, the economic analysis has not been independently evaluated.
- 4.5 A summary of the key matters to be addressed by the resubmission is presented in Table 1.

**Table 1: Summary of key matters to be addressed – economic model**

Matter of concern from the November 2021 submission	Resubmission	Addressed?
<p><b>Placebo response rate:</b> While the PBAC considered that a placebo response rate of 27.8% reflected the primary analysis of the DAPPER study (paragraph 6.52, November 2021 PBAC PSD), it acknowledged that DAPPER was a withdrawal study and there was limited evidence to determine a more accurate estimate of the incremental benefit. The PBAC considered that a placebo response rate of 18%, as proposed by the Sponsor in the pre-PBAC response from a supportive analysis from the DAPPER CSR in which the 3TUG result was treated as a continuous response, was acceptable (paragraph 7.10, November 2021 PBAC PSD).</p>	<p>The resubmission used a placebo response rate of 18%, as updated in the pre-PBAC response for the November 2021 submission and accepted by the PBAC.</p>	<p>Yes</p>
<p><b>Utility value for non-responders:</b> The PBAC noted that the respecified model provided with the pre-PBAC response did not update the utility value for the non-responder health state as recommended by ESC (0.31), but retained the value of 0.122 based on small Sponsor-initiated surveys. The Sponsor argued that the 0.31 utility score reported by Harms et al (2012) was not a suitable proxy for the non-responder health state because it did not reflect an untreated health state. While the PBAC considered the utility gain associated with treatment remained uncertain, it accepted a value of 0.122 (paragraph 7.10, November 2021 PBAC PSD).</p>	<p>The resubmission used a utility value for non-responders of 0.122, as proposed in the November 2021 submission, maintained in the pre-PBAC response, and accepted by the PBAC. The unrounded value derived from the patient survey results should be used in the calculations (see Table 2).</p>	<p>Yes</p>
<p><b>Dose escalation:</b> The PBAC noted that the model assumed that benefits of amifampridine treatment would commence immediately, and agreed with the ESC that a 3 month escalation period would be appropriate, and given the trial data, should not be more than 6 months. However, the PBAC acknowledged the argument in the pre-PBAC response, that dose escalation occurs gradually in clinical practice, and the escalation period in the submission was based on the results of a patient survey. The PBAC considered that dose escalation from 2.5 to 6.85 tablets per day over 66 cycles, as per the November submission, was acceptable (paragraph 7.10, November 2021 PBAC PSD).</p>	<p>The resubmission used a dose escalation period of 66 months, as proposed in the November 2021 submission, maintained in the pre-PBAC response, and accepted by the PBAC.</p>	<p>Yes</p>
<p><b>Amifampridine response rate:</b> The PBAC considered that an amifampridine response rate of 89%, based on a proxy for an assumed discontinuation rate of 11%, was reasonable (paragraph 7.10, November 2021 PBAC PSD).</p>	<p>The resubmission used an amifampridine response rate of 89%, as updated in the pre-PBAC response for the November 2021 submission and accepted by the PBAC.</p>	<p>Yes</p>
<p><b>ICER:</b> The PBAC considered that the ICER should be less than \$85,000/QALY gained, using the assumptions presented in the pre-PBAC response for the November submission (para 7.10, November 2021 PBAC PSD).</p>	<p>The resubmission presented an ICER that was consistent with the PBAC request once the revised price from the pre-PBAC response for the resubmission was applied.</p>	<p>Yes</p>

ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; 3TUG = Triple Timed Up and Go.

4.6 A summary of model changes in the resubmission is provided in Table 2.

**Table 2: Summary of model changes**

Component	November 2021 submission			Resubmission
	Submission Base Case (evaluator corrected model)	ESC re-specification (evaluator corrected model)	Pre-PBAC response (evaluator corrected model)	
(A) Utility values – non-responders	0.122	0.31	0.122	0.122 <sup>a</sup>
(B) Response rate – on treatment	100%	89%	89%	89%
(C) Response rate - placebo	10%	27.8%	18%	18%
(D) Dose escalation	Over 66 months	Over 3 months	Over 66 months	Over 66 months <sup>b</sup>

a. Unrounded value used in Nov 21 evaluator model, see EQ-5D-5L scores tab in Excel model.

b. After updating the Parameters(rev) sheet, Column V in the Ruzurgi (rev) sheet must be updated to reflect the dose escalation period.

- 4.7 The resubmission presented a cost-utility analysis of amifampridine versus placebo for the treatment of patients with LEMS. The comparison was based on the DAPPER trial and data from Sponsor-initiated surveys.
- 4.8 The resubmission nominated a price reduction compared with the November 2021 submission that generated an ICER of \$75,000 to < \$95,000/quality adjusted life year (QALY) gained. This was consistent with PBAC advice for the November 2021 consideration, that that the cost effectiveness of amifampridine would be considered acceptable if the pre-PBAC response assumptions were used and the ICER was less than \$85,000/QALY gained (paragraph 7.10, November 2021 PBAC PSD); however, the Sponsor did not use the model containing corrections performed during the evaluation of the submission considered at the November 2021 PBAC meeting and provided to the Sponsor. Using the evaluation model and the pre-PBAC response assumptions, the ICER would be \$75,000 to < \$95,000/QALY at the Sponsor’s proposed cost per tablet of \$| (dispensed price for maximum quantity [DPMQ] of \$| for 2 packs). To achieve an ICER of less than \$85,000/QALY, the cost per tablet would be \$|. This revised cost corresponds to an ex-manufacturer price (EMP) of \$| per 100 tablet pack and a DPMQ of \$| (for 2 packs).
- 4.9 The results of the economic evaluation are presented in Table 3, incorporating the price adjustment to achieve an ICER of less than \$85,000/QALY as agreed to in the pre-PBAC response.

**Table 3: Results of the economic evaluation**

Resubmission base case	Amifampridine	Placebo	Increment
Costs (\$)			
QALYs	4.99	1.65	3.33
<b>Incremental cost per QALY gained (\$)</b>			<b>1</b>

Source: 'Ruzurgi in LEMS S3 workbook (final)', 'Results' sheet, revised in accordance with pre-PBAC response.

QALYs = quality adjusted life years.

The redacted values correspond to the following ranges:

1\$75,000 to < \$95,000

### Drug cost/patient/year

4.10 The estimated drug cost per patient per year of amifampridine is \$█, based on the proposed price (DPMQ \$█ for 200 tablets) and the recommended dosage regimen (maximum total daily maintenance dose of 100 mg). If the trial mean dose per day is used (67.85 mg), the estimated drug cost per patient per year is \$█.

### Estimated PBS utilisation and financial implications

4.11 A summary of the key matters to be addressed by the resubmission is presented in Table 4.

**Table 4: Summary of key matters to be addressed – financial implications**

Matter of concern	Resubmission	Addressed?
Recalculation of the financial implications using the revised amifampridine price (para 7.12, November 2021 PBAC PSD).	Presented revised financial estimates using the proposed price (DPMQ of \$█ for 200 tablets). However, the estimates required amendment to reflect the price required to satisfy an ICER <\$85,000 (DPMQ \$█ for 200 tablets), which was acknowledged in the Pre-PBAC response.	Yes

DPMQ = dispensed price for maximum quantity; ICER = incremental cost effectiveness ratio.

4.12 All parameters used to calculate the financial impact of amifampridine in the resubmission were the same as for the November 2021 submission, with the exception of the amifampridine proposed DPMQ.

4.13 The estimated net financial impact to the PBS/RPBS for the listing of amifampridine based on the pre-PBAC response price (DPMQ \$█) is \$10 million to <\$20 million over six years (Table 5). This compares to an estimated net financial impact of \$20 million to <\$30 million over six years for the November 2021 submission.

4.14 Consistent with the November 2021 submission, the resubmission assumed no change to MBS costs resulting from the proposed listing of amifampridine.

**Table 5: Estimated utilisation and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Number of scripts dispensed	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
<b>Estimated financial implications of amifampridine</b>						
Net cost to PBS/RPBS (resubmission) (\$)	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Net cost to PBS/RPBS (Pre-PBAC response <sup>a</sup> ) (\$)	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>November 2021 submission estimated utilisation and cost of amifampridine<sup>b</sup></b>						
Net cost to PBS/RPBS (\$)	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>

Source: Table 4.7 (p24) of the resubmission and Table 16, November 2021 PBAC PSD.

DPMQ = dispensed price for maximum quantity

<sup>a</sup> Corresponds to DPMQ proposed in Pre-PBAC response (see paragraph 4.8).

<sup>b</sup> The costs of amifampridine do not take into account the price reduction offered in the November 2021 pre-PBAC response.

The redacted values correspond to the following ranges:

<sup>1</sup>< 500

<sup>2</sup>500 to < 10,000

<sup>3</sup>\$0 to < \$10 million

For more detail on PBAC's view, see section 5 PBAC outcome.

## 5 PBAC Outcome

- 5.1 The PBAC recommended the listing of amifampridine with an Authority Required listing (Telephone/Online) for the treatment of Lambert-Eaton myasthenic syndrome (LEMS). The resubmission provided a revised economic model and financial estimates in response to previous concerns raised by the PBAC. The PBAC considered the revised incremental cost-effectiveness ratio (ICER) was acceptable for the proposed indication, in the context of LEMS being a rare condition with an unmet need for effective treatment. The PBAC noted that the financial estimates had been recalculated, consistent with previous advice. Overall, the PBAC considered that the concerns raised at the November 2021 meeting had been sufficiently addressed.
- 5.2 The PBAC was satisfied that amifampridine provides, for some patients, a significant improvement in efficacy over placebo. The PBAC recalled from its November 2021 consideration that a claim of superior comparative effectiveness was reasonable for amifampridine compared with placebo, however the magnitude of the effect was uncertain due to the limitations of the available clinical evidence. The PBAC considered that amifampridine was inferior to placebo in terms of comparative safety (paragraph 7.8, amifampridine PSD, November 2021 PBAC meeting).
- 5.3 The PBAC noted that the proposed restriction would allow treatment of patients with either paraneoplastic LEMS (pLEMS) or autoimmune LEMS (aLEMS), and considered this was appropriate (see paragraph 3.5).
- 5.4 The PBAC noted that the pre-PBAC response for the resubmission provided a price reduction resulting in an ICER of \$75,000 to <\$95,000 /QALY, consistent with PBAC advice from its November 2021 consideration that the cost effectiveness of amifampridine would be considered acceptable if the pre-PBAC response assumptions were used and the ICER was less than \$85,000/QALY gained. The PBAC recalled that this ICER was acceptable in the context of LEMS being a rare condition with an unmet need for effective treatment.
- 5.5 The PBAC noted that the resubmission had provided revised financial estimates using the revised amifampridine price, as requested. The estimated net financial impact to the PBS/RPBS for the listing of amifampridine was \$10 million to < \$20 million over six years, based on the pre-PBAC response price.
- 5.6 The PBAC recommended that amifampridine should not be treated as interchangeable with any other drugs.
- 5.7 The PBAC advised that amifampridine is not suitable for prescribing by nurse practitioners, given the restriction requirement for prescribing by a clinical immunologist, a neurologist, or a medical practitioner working under the direct supervision of one of these mentioned specialists.

- 5.8 The PBAC recommended that the Early Supply Rule should apply to amifampridine.
- 5.9 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for amifampridine:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies, on the basis of the clinical evidence considered at the November 2021 meeting;
  - b) The treatment is not expected to address a high and urgent unmet clinical need because the drug has been used in clinical practice for many years;
  - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 5.10 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## **6 Recommended listing**

- 6.1 Add new medicinal product as follows:

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
AMIFAMPRIDINE					
amifampridine 10 mg tablet, 100	NEW	2	200	5	Ruzurji
				Early Supply Rule applies? Y	
<b>Restriction Summary / Treatment of Concept: [New 1]</b>					
<b>Concept ID</b> (for internal Dept. use)	<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 – (telephone/online PBS Authorities system)				
	<b>Indication:</b> Lambert-Eaton myasthenic syndrome (LEMS)				
	<b>Clinical criteria:</b>				
	The condition must not be any of: (i) myasthenia gravis, (ii) Guillain-Barre syndrome				
	<b>Treatment criteria:</b>				
	Must be treated by a prescriber type identifying as at least one of the following: (i) a clinical immunologist, (ii) a neurologist, (iii) a medical practitioner working under the direct supervision of one of these mentioned specialists				
	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.				
	<b>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.				

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

## 7 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.

## 8 Sponsor's Comment

The sponsor had no comment.