

## 5.02 AMIFAMPRIDINE, Tablet 10 mg, Ruzurgi<sup>®</sup>, The Trustee for Orspec Pharma Unit Trust

### 1 Purpose of submission

- 1.1 The Category 1 submission requested an Authority Required listing (in writing) for amifampridine for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and children aged 6 years and above.
- 1.2 Listing was requested on the basis of a cost-utility analysis versus placebo. The key components of the clinical issues addressed by the submission are summarised below. (Table 1).

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

Component	Description
Population	Patients (≥ 6 years old) with confirmed Lambert-Eaton myasthenic syndrome (LEMS) including paraneoplastic LEMS (pLEMS) and autoimmune LEMS (aLEMS)
Intervention	Amifampridine (3,4-diaminopyridine or 3,4-DAP) 10 mg tablets
Comparator	Placebo
Outcomes	Symptomatic relief from the weakness associated with LEMS: Triple Timed-up-and-GO (3TUG) test, Quantitative Myasthenia Gravis (QMG), Subject Self-Assessment of LEMS-Related Weakness (W-SAS), Compound muscle action potential (CMAP), Lower Extremity Function Scale (LEFS), LEMS-related activities of daily living (ADLs)
Clinical claim	In patients (≥6 years old) with confirmed LEMS including pLEMS and aLEMS, amifampridine has superior clinical efficacy and superior safety outcomes compared with placebo.

Source: Table 1.2, p14 of the submission and page 121 of the submission. Amended during evaluation.

### 2 Background

#### Registration status

- 2.1 Amifampridine (Ruzurgi<sup>®</sup> 10 mg tablet) is approved by the TGA for the treatment of LEMS and was listed on the Australian Register of Therapeutic Goods (ARTG) on 14 September 2021. The TGA indication is:
- RUZURGI is indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and children aged 6 years and above.
- 2.2 The dossier was submitted to the TGA in October 2020 as an Orphan Drug with priority review status.
- 2.3 The current application for amifampridine (Ruzurgi) is for the free base form of 3,4-diaminopyridine. Amifampridine (Ruzurgi) has also been approved for use in Canada. A different formulation, the phosphate salt of amifampridine (which has the chemical name 3,4-diaminopyridine phosphate), was approved in Europe (in 2009), the US (in 2018) and Canada (in 2020) and has the trade name Firdapse<sup>®</sup>. Currently,

there is no direct comparison between the two formulations (free base and phosphate salt) to establish equivalence in terms of effectiveness and safety.

- 2.4 Amifampridine has been used in global clinical practice for many years (granted orphan drug status in the US in 1990) for LEMS without high quality evidence. In Australia amifampridine has been used for about 15 years under the Special Access Scheme (SAS). The ESC noted that amifampridine may also be supplied by authorised medical practitioners via the Authorised Prescriber (AP) scheme, and that amifampridine is included in the list of medicines with an established history of use under that scheme.
- 2.5 The PBAC noted that amifampridine is available via the SAS, however considered that some LEMS patients experience access challenges. The PBAC considered that PBS listing would improve equity of access for patients, especially for those living in regional areas.

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

### 3 Requested listing

- 3.1 The requested listing is presented below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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	Ruzurgi
<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 – <del>in writing</del> (telephone/online PBS Authorities system)					
<b>Administrative Advice:</b> <i>No increase in the maximum quantity or number of units may be authorised.</i>					
<b>Administrative Advice:</b> <i>No increase in the maximum number of repeats may be authorised.</i>					
<b>Administrative Advice:</b> <i>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.</i>					
<b>Indication:</b> <del>Amifampridine is indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and children aged 6 years and above</del>					
<b>Condition:</b> Lambert-Eaton myasthenic syndrome (LEMS)					
<b>Treatment Phase:</b> [blank] <del>Initial treatment of weakness associated with LEMS</del>					
<b>Population criteria:</b> <del>Amifampridine must not be given to children under the age of 6</del> <i>Patient must be each of: (i) untreated with this drug, (ii) diagnosed with the condition stated in the PBS indication; or</i> <i>Patient must be continuing PBS-subsidised treatment with this drug; or</i>					

<i>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;</i>
<b>Clinical criteria:</b>
<del>The patient must have weakness associated with LEMS</del>
<b>AND</b>
<b>Clinical criteria:</b>
<del>The patient must not have a history of seizures</del>
<b>AND</b>
<b>Clinical criteria:</b>
<del>The patient must not have a hypersensitivity to amifampridine or another aminopyridine</del>
<b>Clinical criteria:</b>
<del>The condition must not be any of: (i) myasthenia gravis, (ii) Guillain-Barre syndrome</del>
<b>Treatment criteria:</b>
<del>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</del>

<del><b>Treatment phase:</b> Continuing treatment – Patient must have previously received PBS-subsidised treatment with an authority prescription for this drug for the treatment of weakness associated with LEMS</del>
<b>Clinical criteria:</b>
<del>Patient must demonstrate a clinically meaningful response to the initial treatment as determined by the treating clinician</del>

<del><b>Treatment phase:</b> Grandfather treatment – Transitioning from non-PBS to PBS-subsidised supply for the treatment of weakness associated with LEMS</del>
<b>Clinical criteria:</b>
<del>The patient must have weakness associated with LEMS</del>
<b>AND</b>
<b>Clinical criteria:</b>
<del>The patient must not have a history of seizures</del>
<b>AND</b>
<b>Clinical criteria:</b>
<del>The patient must not have a hypersensitivity to amifampridine or another aminopyridine</del>

- 3.2 The submission proposed an ex-manufacturer price of \$ [REDACTED] per pack of 100 tablets (10 mg tablets).
- 3.3 The restriction differs from the clinical algorithm presented (Figure 1). The clinical algorithm indicates that only patients with moderate or severe weakness are recommended to receive amifampridine, whereas patients with mild symptoms should receive treatment for malignancy (if present) and monitor LEMS symptoms. There was no information in the submission about how to define “moderate or severe weakness”. The proposed restriction did not include an indication of the severity of the condition. The Pre-Sub-Committee Response (PSCR) clarified that Weinberg

(2021)<sup>a</sup> described mild weakness as having no functional impact, whereas moderate to severe weakness interferes with patient function. The Pre-PBAC response stated that inclusion of a requirement for “moderate to severe weakness” in the restriction is appropriate, but did not state how it should be defined or measured.

- 3.4 The requested continuing criteria requires that the patient demonstrate a clinically meaningful response to the initial treatment as determined by the treating clinician. The definition of a clinically meaningful response is unclear. This could include the Triple Timed Up and Go (3TUG) test or the Quantitative Myasthenia Gravis (QMG) score which were used as the main effectiveness outcomes in the trials presented in the submission. It should however be noted that 3TUG test requires patients to be ambulatory. Alternative criteria may include the Medical Research Council (MRC) Scale for Muscle Strength used by the National Blood Authority to determine qualifying criteria for intravenous immunoglobulin (IVIg) therapy for LEMS. While the ESC noted that it may be reasonable to allow continuing treatment at the discretion of the prescriber, with the financial impact managed by a risk sharing arrangement (RSA) and/or Quality Use of Medicines (QUM) initiatives, it also considered that it may be reasonable to refer to a scale to qualify for continuing treatment, with clinicians likely to adopt this in practice since the Scale for Muscle Strength is used in LEMS patients to access IVIg. The Pre-PBAC response stated that it would be inappropriate to restrict ongoing use based on a specific scale, and treatment should be continued at the discretion of the prescriber.
- 3.5 The submission requested initial, continuing and grandfather listings for treatment of weakness associated with LEMs. The Secretariat noted that if treatment is continued at the discretion of the prescriber, all the treatment phases can be combined into a single restriction, as shown in the listing proposed by the Secretariat.
- 3.6 LEMS is a rare condition and patients are likely to be managed by neurologists and immunologists, and therefore the treatment criteria should reflect this. The PSCR agreed with the evaluation that it would be appropriate for amifampridine to be prescribed by a neurologist or immunologist. The PBAC considered it would be appropriate to add “treated by a neurologist or immunologist” to the treatment criteria.
- 3.7 With respect to patient age, the evidence presented in the submission (patients aged 18 years or over) was not consistent with the requested listing (from 6 years of age and above). LEMS rarely affects paediatric patients and thus there was insufficient data in terms of clinical effectiveness or safety among paediatric populations. The PBAC considered that patient age is not required to be specified in the restriction.

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<sup>a</sup>Weinberg (2021). Lambert-Eaton myasthenic syndrome: treatment and prognosis. UpToDate, Inc., accessed 20 September 2021.

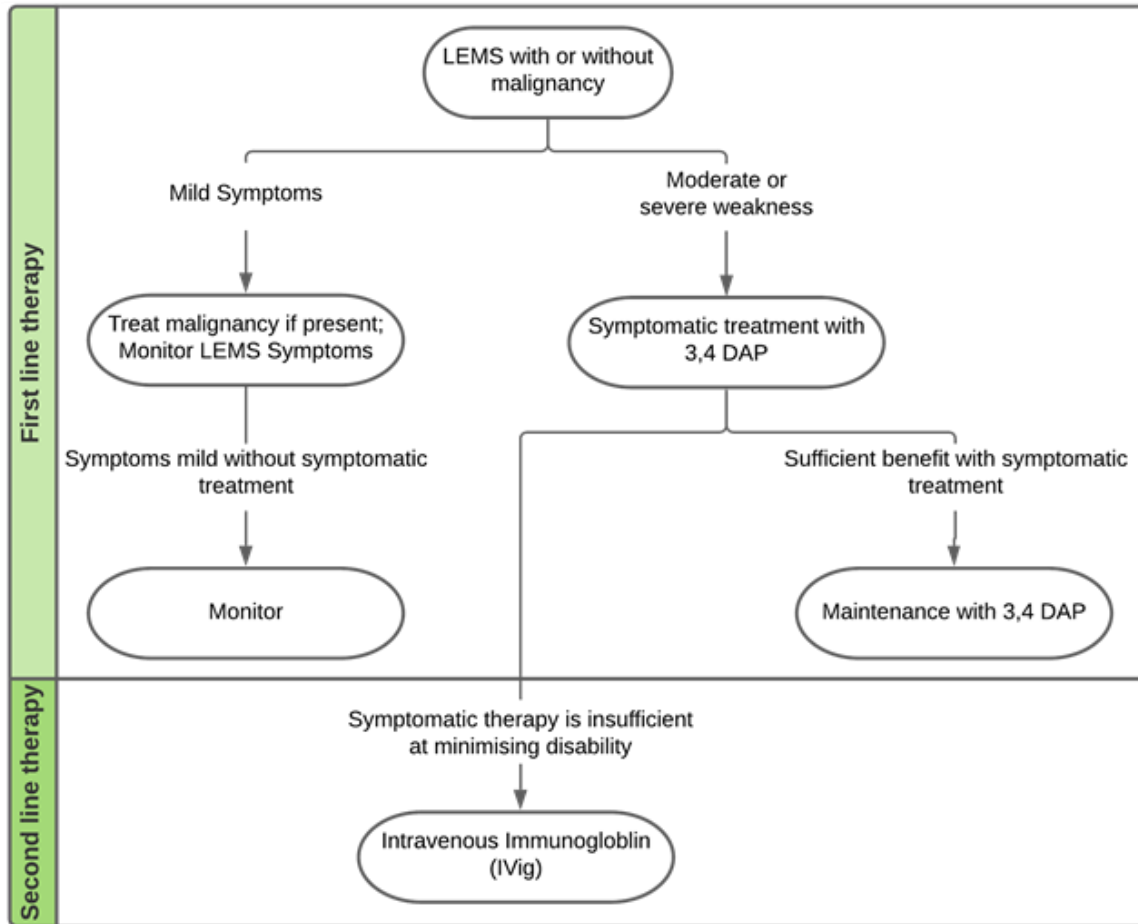
- 3.8 The ESC noted that LEMS symptoms may overlap with myasthenia gravis symptoms but potential points of difference include autonomic symptoms and in ocular presentations.
- 3.9 The PBAC considered that a written authority may not be required, and the telephone/online PBS Authorities system would be appropriate based on the proposed criteria, if prescribing is limited to specialist prescribers (see paragraph 3.6).

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

## **4 Population and disease**

- 4.1 LEMS is a rare condition in which progressive muscle weakness results from deficient acetylcholine release from presynaptic terminals of neuromuscular junctions. There are limited data available for the Australian LEMS population. The submission stated that the number of prevalent LEMS patients could range from 11 to 192. However, the source of this was not provided and could not be verified. The estimates from global prevalence literature indicate prevalence between 1.8 and 10.9 per million, translating to a range between 44 and 269 patients in Australia. The upper estimate is based on reported crude prevalence of 10.9 per million from Abenroth et al (2017). There is a wide range in the prevalence estimates and it remains very uncertain.
- 4.2 LEMS can be classified as autoimmune (50%) or paraneoplastic (50% of patients) arising from small cell lung carcinoma (SCLC). Only 3% of those in the DAPPER trial and 35% of those in the DUKE trial had a diagnosis of paraneoplastic LEMS. Thus, there is less certainty of the clinical effectiveness of amifampridine in paraneoplastic LEMS and therefore if the trial results are applicable to the Australian LEMS population.
- 4.3 The most common presentation is progressive proximal muscle weakness, affecting the hip girdle more than the shoulder. As mobility becomes more impaired, basic activities of daily living deteriorate. Patients have a characteristic waddling gait and many are unable to climb stairs and some become bedridden and require mechanical ventilation and tube feeding. Autonomic dysfunction presents with dry mouth, impotence and constipation. Paraneoplastic LEMS patients typically present with neurological symptoms before their cancer is diagnosed.
- 4.4 In terms of the level of disability associated with LEMS, data from a sample of 14 Australian patients with LEMS were used to calculate the health-related quality of life (HRQoL) utility score prior to treatment (0.122). The pivotal DAPPER study for the submission indicated that 41% of patients had been hospitalised due to LEMS.
- 4.5 Amifampridine is proposed as the first line symptomatic treatment of muscle weakness for LEMS.
- 4.6 Figure 1 presents the proposed clinician management algorithm in Australia.

Figure 1: Predicted clinical management algorithm in Australia



Source: Figure 1.3, p32 of the submission.

3,4 DAP = 3,4-diaminopyridine (amifampridine); LEMS = Lambert-Eaton myasthenic syndrome; IVIg = intravenous immunoglobulin

4.7 The evaluation commented that the submission did not provide a verifiable source for the proposed treatment algorithm shown in Figure 1. The PSCR clarified that clinical guidelines from UptoDate (Weinberg 2021) and the National Blood Authority (NBA)<sup>b</sup> for the use of IVIg for LEMS were used to build the clinical algorithm. The ESC noted that the proposed treatment algorithm associates mild LEMS symptoms with malignancy, but patients with malignancy may also present with moderate or severe LEMS symptoms.

4.8 The ESC also noted that other medications such as pyridostigmine and immunomodulators/suppressants are not represented in the algorithm, and that patients may use amifampridine in addition to other medications. The pre-PBAC response stated that feedback was sought from experienced clinicians regarding expected changes to the use of other therapies, should amifampridine be PBS listed.

<sup>b</sup>National Blood Authority (2018). Criteria for Clinical Use of Immunoglobulin in Australia: (Lambert-Eaton Myasthenic Syndrome). In National Blood Authority Australia (Vol. 3).

The pre-PBAC response stated that variability of effectiveness with other treatments, notably IVIg, was consistently reported, and that the use of amifampridine would be expected to be associated with a reduction in use of IVIg. The pre-PBAC response also referred to the consumer comments, which were consistent with this advice (see paragraphs 6.2 to 6.6). The PBAC considered that concomitant therapies (such as IVIg) are not anticipated to change substantially. Although it may be reasonable to expect some reduction in use of IVIg, PBAC considered the magnitude of the impact to be uncertain given that patients are already accessing amifampridine via SAS. The ESC noted the importance of treating the underlying malignancy first (if present), as it may be the only intervention necessary to produce improvement in neurologic symptoms (Weinberg 2021).

- 4.9 The ESC noted that summary statistics were provided by the NBA to inform the PBAC of utilisation of IVIg for LEMS over the last 3 years. In the 2020-2021 financial year, the total number of patients treated with IVIg for LEMS was approximately 40 (the exact number could not be reported due to privacy requirements). The average patient age and weight were reported to be 65 years and 72 kg, respectively. Similar utilisation statistics were seen in the previous two years. The ESC considered that insufficient information was provided in the submission about the potential changes to IVIg use if amifampridine is PBS listed (see paragraph 6.53).

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

## **5 Comparator**

- 5.1 The submission nominated standard medical management as the comparator, which was represented in the key clinical evidence as placebo. Other medications such as pyridostigmine or IVIg may be commonly used in the absence of access to amifampridine. It is unclear how amifampridine would replace or affect the doses of the current standard-of-care treatment.
- 5.2 The PSCR noted that there are no registered treatments in Australia for patients with LEMS. It stated that IVIg is recommended by the NBA as a second line treatment following symptomatic therapy (shown as 3,4-DAP [amifampridine] in Figure 1) that is insufficient at minimising disability. However, the PSCR also stated that if the patient is unable to access amifampridine, then LEMS patients may receive IVIg if pyridostigmine is insufficient in improving LEMS-related weakness (under these circumstances, the PSCR described IVIg as a first line treatment, although the ESC noted that other medications such as pyridostigmine and immunomodulators/suppressants [see paragraph 4.8] are not represented in the algorithm). The PSCR also stated that in practice, other medicines are used as complementary treatments to amifampridine, and that a multifactorial approach is used to treat complex symptoms. The ESC noted that of patients in the DAPPER trial, only one patient was taking amifampridine alone and all other trial participants were taking a combination of medications that included pyridostigmine and/or

immunomodulators/suppressants in addition to amifampridine (see paragraph 6.21). The ESC highlighted that comparative evidence against these other medications is limited and unlikely to change.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

6.1 There was no hearing for this item.

### ***Consumer comments***

6.2 The PBAC 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.

6.3 The HCP noted the rarity of LEMS but stated that diagnosis can usually be reached with certainty. The HCP described the positive impact that amifampridine has on muscle strength and quality of life for patients receiving treatment, and how they rely on it for their daily function. The HCP stated that amifampridine is generally well tolerated and appears to be without major long-term side effects or challenges in its prescribing.

6.4 The PBAC noted the advice received from Myasthenia Alliance Australia (MAA) clarifying the likely use of amifampridine in clinical practice. The MAA stated that feedback from people suffering with LEMS indicated that amifampridine is effective for a range of users and the free base form appears well tolerated. The MAA also shared concerns that not having access to amifampridine would be detrimental to health outcomes and quality of life. The MAA stated that some patients struggle with current access, which is hospital based and subject to repeat authorisation from a select group of specialist HCPs, and patients must then liaise with the hospital pharmacy to obtain the medication. The MAA noted these difficulties are compounded for those living in regional areas, given the effects of the condition and the impact of travelling and attending appointments. The MAA stated that access via the PBS would provide a much improved outcome. The PBAC noted that this advice was supportive of the evidence provided in the submission.

6.5 Nine individuals (9) currently receiving amifampridine provided insight into patients' experience with LEMS and treatment with this medicine. Common debilitating LEMS symptoms were described as muscle weakness/fatigue, speech disturbance, blurred vision, difficulty swallowing, lack of balance, difficulty standing or walking, inability to move even in bed, dry mouth, and drooping head and eyelids. Patients described repeated falls, emergency attendances and hospitalisations, confinement to a wheelchair and a requirement for full time care. When provided with amifampridine tablets, patients described their symptoms improving almost immediately and having

instant relief, accompanied by a dramatic improvement in quality of life and a return to work and family life. A strong preference for access to be available through local pharmacies was also expressed.

- 6.6 In their testimonials, patients also described other medications they had received for LEMS treatment. A common theme was prior infusions with IVIg not being effective and accompanied by sometimes severe side effects (headaches). Patients also described damaged/collapsed veins with prolonged IVIg treatment. Several patients mentioned that optimal treatment for them involved a combination of amifampridine and pyridostigmine, although emphasised that pyridostigmine alone was insufficient as an effective treatment.

### **Clinical trials**

- 6.7 The submission was based on two small randomised, double-blind, placebo-controlled, trials: DAPPER (published in 2018) and DUKE (published in 2000).
- 6.8 Details of the trials presented in the submission (DAPPER and DUKE) are provided in Table 2. Additional supportive evidence was provided by three randomised studies reporting improvements in clinical and electrophysiological endpoints to a maximum of 16 days follow up.

**Table 2: Trials and associated reports presented in the submission**

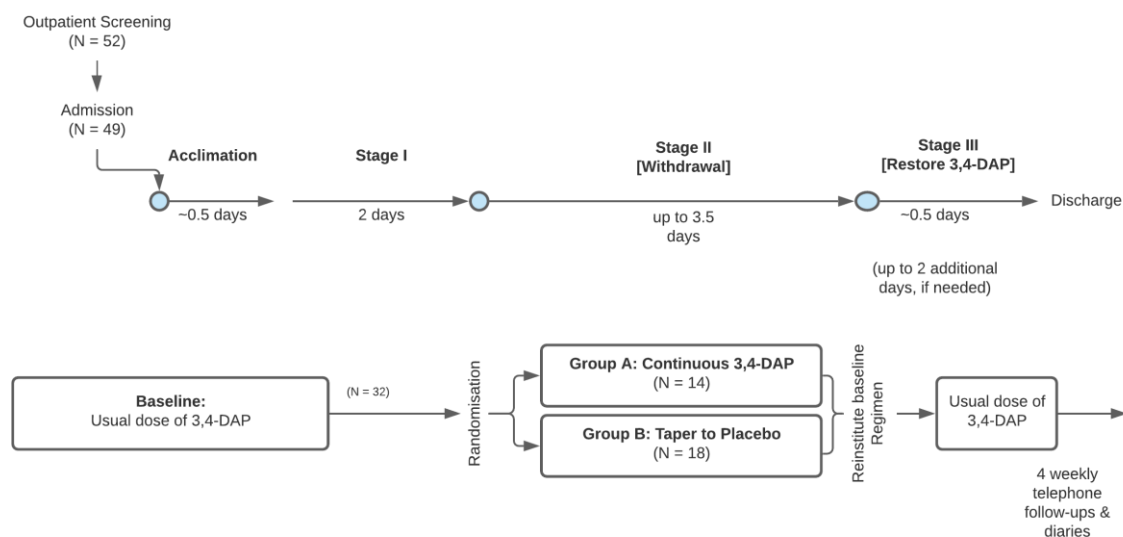
<b>Trial ID</b>	<b>Protocol title/ Publication title</b>	<b>Publication citation</b>
DAPPER Study	NCT01511978 Inpatient Double-Blind Placebo-Controlled Withdrawal Study of 3,4-Diaminopyridine Base (3,4-DAP) in Subjects with Known Lambert-Eaton Myasthenic Syndrome (LEMS)	Clinical Study Report Jacobus Pharmaceutical, 2012
	<u>Key Publication</u> Sanders et al., 2018 3,4-diaminopyridine base effectively treats the weakness of Lambert-Eaton myasthenia.	Sanders DB, Juel VC, Harati Y, Smith AG, Peltier AC, Marburger T, Lou JS, Pascuzzi RM, Richman DP, Xie T, Demmel V, Jacobus LR, Aleš KL, Jacobus DP; Dapper Study Team. Muscle Nerve. 2018 Apr;57(4):561-568. doi: 10.1002/mus.26052. Epub 2018 Feb 2. PMID: 29280483; PMCID: PMC5900968.
	<u>Conference abstract</u> Sanders et al., 2015 Results of a double-blind placebo-controlled study of 3,4-diaminopyridine (DAP) in lambert-eaton myasthenic syndrome (LEMS)	Sanders DB, Juel VC, Harati Y, Smith AG, Peltier A, Marburger T, Lou J-S, Pascuzzi RM, Richman DP, Xie T, Jacobus LR, Ales KL, Jacobus DP. Annals of neurology 2015; 78(null): S104.
Duke Study	NCT00004832 Randomized Study of 3,4-Diaminopyridine for Lambert-Eaton Myasthenic Syndrome	JPC 3,4-DAP DUKE RCT SUPPLEMENT Jacobus Pharmaceutical Company, Inc
	<u>Key Publication</u> Sanders et al., 2000 A randomized trial of 3,4-diaminopyridine in Lambert-Eaton myasthenic syndrome	Sanders DB, Massey JM, Sanders LL, Edwards LJ. Neurology. 2000 Feb 8;54(3):603-7. doi: 10.1212/wnl.54.3.603. PMID: 10680790.

Source: Table 2.4, pp46-47 of the submission.

- 6.9 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.

- 6.10 The DAPPER trial was a Phase 2, randomised, double-blind, placebo-controlled, withdrawal study to evaluate efficacy and safety of amifampridine in subjects with LEMS (N=32; 18 taper to placebo) (Figure 2). Patients (recruited in the USA) on a steady dose of amifampridine for at least three continuous months were eligible, if they were responsive to amifampridine, as defined by 3TUG testing before and after the first doses of the morning, afternoon, and evening. Patients were randomised to stay on their current dose or withdraw from amifampridine (tapering to placebo up to 3.5 days).

Figure 2: Study design schematic for DAPPER trial



Source: Figure 2.3, p50 of the submission

3,4 DAP = 3,4-diaminopyridine; N = total participants in group

- 6.11 The DUKE trial was a prospective, placebo-controlled, randomised study to evaluate the effectiveness of amifampridine in patients with LEMS and to determine the acute and long-term side effects of amifampridine (N=26). Eligible subjects received 10 to 20 mg of amifampridine or placebo 3 or 4 times a day for 6 to 9 days during the blinded portion of the study, after which subjects received open-label amifampridine.
- 6.12 Given the short duration of the trials (less than 1 week), there are limited data regarding the durability of amifampridine in a trial setting. The DUKE study had an open-label phase for 25 patients up to 6 months.
- 6.13 The trials allowed for co-administration with other medications. The ESC noted that the doses of other LEMS-related medications were stabilised 3 months prior to inclusion in the DAPPER trial and considered the impact on the relative effectiveness may not be substantial, albeit unquantifiable from the data provided.
- 6.14 The key features of the DAPPER and DUKE trials are summarised in Table 3.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Amifampridine vs. Placebo</b>						
DAPPER	32	R, DB / up to 3.5 days	High	Stable on amifampridine for at least 3 months before enrolment	Response rate (degree of change in 3TUG test <sup>a</sup> )	Assumed 100% response rate
DUKE	26	R, DB / 6-9 days / 24-hour washout followed by 24-hour observation	Medium	Treatment naïve	Response rate (change from baseline QMG)	Assumed 100% response rate

<sup>a</sup> The 3TUG test was performed 6 times per day (15 minutes prior to and about 2 hours after the first dose after 12 am, the first dose after 12 pm, and the first dose after 5 pm).

Source: Table 2.5, p48 of the submission.

3TUG = Triple Timed-Up-and-Go; DB = double blind; QMG= Quantitative Myasthenia Gravis; R = randomised.

- 6.15 In the DAPPER trial, 52 patients were screened and 32 were eligible and randomised into the trial. Twenty patients were found to be ineligible due to insufficient response to 3TUG during screening assessments (n=18); or failed drug screen (n=2).
- 6.16 In the DUKE trial, 37 patients were eligible, but 11 were not randomised (7: QMG Score > 5; 1: atrial fibrillation; 1: compressive fracture; 1: non-compliant; 1: receiving chemotherapy).
- 6.17 For the DAPPER trial, while there is low risk of selection bias (due to randomisation), there is high risk of sampling bias given that eligible patients were those who successfully responded to amifampridine for at least three months before randomisation. This may overestimate the effect of amifampridine since patients who did not respond or had less response to amifampridine were excluded from the trial. There was also a risk of performance bias where it may not be possible to fully blind the patients and research personnel to placebo. This was evidenced by the higher side-effect profiles reported during the taper-to-placebo phase which may be due to the withdrawal of amifampridine from patients who were successfully using the medication already. Again, this may overestimate the effect of amifampridine if blinding was unmasked. There was low risk for detection, attrition and reporting bias.
- 6.18 For the DUKE trial, there was uncertainty in risk of bias for selection, detection and reporting due to the lack of information provided in the submission or the publication referenced (Sanders et al., 2000). There was a low risk of bias for performance and attrition bias. To be eligible for the trial, the QMG score had to be 5 or more.

### **Comparative effectiveness**

- 6.19 The DAPPER trial reported that none of the patients randomised to continue amifampridine experienced a greater than 30% deterioration in the final post-dose 3TUG test. In contrast, 72% of patients (13/18) randomised to the taper-to-placebo arm experienced a greater than 30% deterioration in the final 3TUG test (Table 4). There was no justification provided in the submission regarding whether the

30% deterioration threshold was clinically meaningful, although Huang et al (2011<sup>c</sup>; identified during the evaluation) reports that a 30% deterioration in 3TUG test is a clinically meaningful threshold in patients with Alzheimer’s disease.

**Table 4: Results of >30% deterioration in the Final Timed up and Go (3TUG) Test for DAPPER trial**

Trial ID	Amifampridine n/N (%)	Taper-to-placebo n/N (%)	Relative risk (95% CI)	Risk difference (95% CI)
DAPPER (Intention to Treat)	0/14 (0)	13/18 (72.2)	<b>0.047 (0.003 to 0.727)</b>	-0.722 (-0.929 to -0.515)

Source: Table 2.19, p78 of the submission. Risk difference calculated as part of evaluation.

CI = confidence interval; n = number of participants with event; N = total participants in group.

Text in bold indicate statistical significance at p-value <0.05.

- 6.20 As the DAPPER trial only included patients who had already responded to amifampridine, the effectiveness of amifampridine is uncertain for those who are naïve to amifampridine.
- 6.21 In addition, patients in the DAPPER trial were receiving a variable mix of other therapies. One subject was on amifampridine alone, 20 subjects were on amifampridine + pyridostigmine, 6 subjects were on amifampridine + pyridostigmine + immunomodulators/immunosuppressants, and 5 subjects were on amifampridine + immunomodulators/immunosuppressants. There was no information provided on the efficacy or safety according to these different groups.
- 6.22 The DUKE trial demonstrated a change in baseline in QMG score of –2.0 in patients who received amifampridine compared to placebo (Table 5). The QMG score improved at least two points in 7 of the 12 patients (58%) who were taking amifampridine, but in none of the patients taking placebo. The use of QMG was designed for patients with myasthenia gravis and may not be appropriate for measuring the impact of muscle weakness related to LEMS, as the QMG score relies on ocular weakness, which is a comparatively minor component of LEMS. It is also not justified whether a change of -2.0 in QMG score is clinically meaningful for patients with LEMS. A study by Barnett et al (2012)<sup>d</sup> identified during the evaluation reports clinically meaningful thresholds for QMG change of >2.6 and 3.5 from separate studies. In the DUKE trial the median QMG score increased by 0.25 points after 6 days in patients on placebo, compared with a reduction (improvement) by 2.0 points among those who received amifampridine. The PSCR stated that a 2-point change is considered clinically significant in mild to moderate myasthenia gravis and, in the absence of specific data in LEMS, is likely to be clinically relevant in the proposed PBS population. This is aligned with the conclusion of the TGA Clinical Evaluation Report

<sup>c</sup> Huang SL, Hsieh CL, Wu RM, Tai CH, Lin CH, Lu WS. Minimal detectable change of the timed "up & go" test and the dynamic gait index in people with Parkinson disease. *Phys Ther.* 2011 Jan; 91(1):114-21.

<sup>d</sup> Barnett C, Katzberg H, Nabavi M, Vrtil V, The Quantitative Myasthenia Gravis Score Comparison with Clinical, Electrophysiological, and Laboratory Markers. *Journal of Clinical Neuromuscular Disease: June 2012 - Volume 13 - Issue 4 - p 201-205.*

which stated that the QMG results of the DUKE trial were statistically significant and clinically relevant in patients treated with amifampridine.

**Table 5: Change from baseline in the Quantitative Myasthenia Gravis (QMG) for DUKE trial**

QMG (intention-to-treat)	Amifampridine (N=12)	Placebo (N=13)	p-Value
Baseline	8.5 (7.3 to 17.0)	12.3 (9.0 to 13.5)	0.625
Post-baseline	6.5 (5.0 6 to 14.3)	12.8 (9.0 to 13.5)	0.156
Change from baseline	<b>-2.0 (-3.0 to 0.0)</b>	<b>0.00 (-1.0 to 1.5)</b>	<b>0.009</b>

Source: Table 2.31 and 2.32, pp92-93 of the submission.

N = total participants in group; QMG= Quantitative Myasthenia Gravis.

Text in **bold** indicate statistical significance at p-value <0.05.

### **Comparative harms**

6.23 In the DAPPER trial, there were reports of treatment-emergent adverse events (TEAEs) (excluding LEMS signs and symptoms) in the amifampridine arm in 5/14 (36%) patients, compared with 12/18 (67%) in the taper-to-placebo arm (Table 6). None of these were severe adverse events (AEs). There were no deaths reported in the study. There were no adverse changes in the clinical laboratory, blood pressure, pulse rate, or ECG parameters attributable to amifampridine or the withdrawal of study drug. The DAPPER trial included patients who were successfully taking amifampridine already, so there was no information on AEs for patients who are naïve to amifampridine. Further, the common co-administration of other medications could affect the evaluation of AEs related to amifampridine.

**Table 6: Summary of key adverse events (AEs) in the DAPPER trial**

Trial ID	Amifampridine n/N (%)	Taper-to-placebo n/N (%)
<b>Subjects with any AEs (including baseline AEs)</b>		
All adverse	7/14 (50)	14/18 (78)
AEs excluding LEMS signs and symptoms	6/14 (43)	12/18 (67)
LEMS signs and symptoms only	2/14 (14)	7/18 (39)
<b>Subjects with treatment-emergent AEs (TEAE)</b>		
All adverse	6/14 (43)	14/18 (78)
AEs excluding LEMS signs and symptoms	5/14 (36)	12/18 (67)
LEMS signs and symptoms only	2/14 (14)	6/18 (33)
<b>Subjects with TEAEs related to taper of study drug</b>		
All adverse	0/14 (0)	2/18 (11)
AEs excluding LEMS signs and symptoms	0/14 (0)	0/18 (0)
LEMS signs and symptoms only	0/14 (0)	2/18 (11)
<b>Subjects with serious TEAEs (SAEs)</b>		
All adverse	0/14 (0)	1/18 (6)
AEs excluding LEMS signs and symptoms	0/14 (0)	1/18 (6)
LEMS signs and symptoms only	0/14 (0)	0/18 (0)
<b>Subjects with SAEs related to withdrawal of study drug</b>		
All adverse	0/14 (0)	0/18 (0)
AEs excluding LEMS signs and symptoms	0/14 (0)	0/18 (0)
LEMS signs and symptoms only	0/14 (0)	0/18 (0)
<b>Subjects who discontinued blinded study drug during Stage II due to a TEAE</b>		
All adverse	0/14 (0)	2/18 (11)
AEs excluding LEMS signs and symptoms	0/14 (0)	0/18 (0)
LEMS signs and symptoms only	0/14 (0)	2/18 (11)

Source: Table 2.24, p85 of the submission.

AE = adverse event; CI = confidence interval; LEMS = Lambert-Eaton myasthenic syndrome; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk; SAE = serious treatment-emergent adverse event; TEAE = treatment-emergent adverse event

- 6.24 While the DUKE trial provided some information on patients who were naïve to amifampridine, the submission did not tabulate the key AEs related to the DUKE trial. Data from Sanders (2000) reported that four (of 14) patients taking blinded amifampridine and 8 (of 22) patients taking open-label amifampridine reported tingling perioral and digital paraesthesia. There were no changes attributable to amifampridine on electroencephalogram or electrocardiogram, or results of blood tests of liver, kidney, hematologic, or endocrine function during the trial or after six months of the open-label phase.
- 6.25 The investigators reported one patient in the DUKE study discontinued amifampridine after 1 week due to lack of apparent benefit. The submission also reported treatment discontinuations for patients treated in the USA between July 2019 and August 2020 based on the Periodic Adverse Drug Experience Report (PADER). The submission reported that of 117 patients (108 adults and 9 paediatrics) receiving amifampridine, two (of 9 paediatric patients, 22%) and 12 (of 108 adult patients, 11%) discontinued amifampridine within the period of the report (approximately one year). This is inconsistent with the assumption in the economic model that the effectiveness of

amifampridine is unchanged throughout the lifetime of an individual using amifampridine (paragraph 6.51).

- 6.26 The submission presented an integrated safety analysis, combining data from the DAPPER and DUKE trials with a retrospective pharmacovigilance review (RPV) of 162 patients in the compassionate use program (referred to as RPV162). The data have a cut-off date of 15th January 2016. The majority (78.4%) of patients receiving amifampridine experienced at least one AE; most were mild (64.6%) or moderate (11.2%) in severity. Treatment-related adverse events were reported in 68 (42%) patients. Most were mild (93%) or moderate (4.5%). One patient experienced a severe AE related to amifampridine (TGA Clinical Evaluation Report, p89). No deaths were reported to be related to amifampridine. The occurrence of AEs is not consistent with the cost-utility analysis, which assumes no AEs in the modelling; however, this may be reasonable given they are largely mild with only 4.5% moderate TEAEs.
- 6.27 The submission also provided information about safety in among an additional 72 patients in the “Special Populations” group (different from the 162 mentioned above). This “Special Populations” group did not exclude patients with seizures, pregnancies, cardiac/renal/hepatic history, suicidal ideation, and also included five paediatric patients. The majority (97.1%) experienced at least one AE: 55.1% were severe and 9% were fatal but none of the deaths were attributed to amifampridine. More than half (57%) had amifampridine adjusted or discontinued due to an AE. Nineteen SAEs (14 patients) were assessed as related to amifampridine, including 8 patients with convulsion and 1 patient each with grand mal convulsion, loss of consciousness, tremor, atrial fibrillation, anxiety, chest pain, fall, and accidental overdose (submission p113). There may be a higher likelihood of AEs and discontinuation when considering a non-trial population of people taking amifampridine, as reflected by the Special Populations group.
- 6.28 In the “Special Populations” group, 27 patients had died by 16 April 2016. The cause of death was unknown/not reported in 12 patients; five patients died of respiratory failure/arrest (one was associated with the progression of lung cancer), and an additional three patients died of metastatic SCLC or its complications. Of the remaining patients who died, 1 subject each died due to complete heart block refusing pacemaker, “long illness,” cardiopulmonary arrest with metastatic lung cancer, myasthenic syndrome, ALS, multi-organ and renal failure, CHF, suicide, marasmus, and kidney failure. None of the deaths was attributed to amifampridine.
- 6.29 The submission stated that amifampridine can cause serious AEs such as seizures and cardiac-related events (e.g. arrhythmias). In the compassionate use program (with a total of 162 patients), 27 patients were identified as having one or more seizure events: 5 patients in RPV162 and 22 from the Special Populations group. In the RPV162 population, the rate of convulsion was 0.7 events per 100 patient-years. The reliability of this estimate is limited by the retrospective nature of the data collection. Most of the seizure events occurred in patients with underlying malignancy and/or

CNS pathology (e.g., CVA, brain or head injury) and/or overdose (either intentional or inadvertent) and/or in the presence of other potentially contributing medications. Evidence from both trials did not identify issues with QTc prolongation. This matches with the warnings on the Product Information.

### **Benefits/harms**

- 6.30 The benefit of amifampridine is to improve muscle weakness in patients with LEMS. The evidence was demonstrated in two trials (DAPPER, DUKE). The DAPPER study demonstrated that withdrawal of amifampridine led to greater muscle weakness (using the 3TUG outcome) (Table 4). The DUKE study demonstrated that amifampridine improved muscle weakness as measured by the QMG score (Table 5). The submission claimed that amifampridine improves quality of life but is not expected to prolong life.
- 6.31 The potential harm of amifampridine is due to its side effect profile, in particular with respect to seizures and cardiac-related events (paragraph 6.29). Amifampridine is reported to have a narrow therapeutic index and supratherapeutic exposure has been associated with an increase in the risk for seizures (Haroldson, Musson, Hanson, Quartel, & O'Neill, 2015).
- 6.32 On the basis of direct comparison evidence presented by the submission (DAPPER trial), for every 100 patients treated with amifampridine in comparison with the taper-to-placebo arm over 3.5 days:
- Approximately 72 fewer patients would have muscle weakness (as determined by >30% deterioration in 3TUG – DAPPER trial; Table 4).
- 6.33 On the basis of direct comparison evidence presented by the submission (DUKE trial), for every 100 patients treated with amifampridine in comparison with placebo over 6 days:
- Approximately 58 additional patients would improve muscle weakness (as determined by at least 2 QMG points; paragraph 6.22).
- 6.34 On the basis of single arm observational evidence (RPV162) presented by the submission, for every 100 patients treated with amifampridine (time period not reported):
- Approximately 1 patient would have a severe AE related to amifampridine (paragraph 6.26).
- 6.35 On the basis of single arm observational evidence (Special Populations group) presented by the submission, for every 100 patients treated with amifampridine (time period not reported), the following patients would have a severe AE related to amifampridine (paragraph 6.27).
- Approximately 8 patients with convulsion.

- Approximately 1 patient each with grand mal convulsion, loss of consciousness, tremor, atrial fibrillation, anxiety, chest pain, fall, accidental overdose (8 patients in total).

### **Clinical claim**

6.36 The submission described amifampridine as superior in terms of effectiveness compared with placebo. The evaluation and ESC considered this claim was partially supported, but the magnitude of the effect was likely overestimated and uncertain. The key issues were:

- Small patient numbers (N=32 for DAPPER; N=26 for DUKE) and short duration of evaluation (up to 3.5 days for DAPPER; 6 days for DUKE). The evaluation noted it is challenging to conduct larger trials due to LEMS being a rare condition, and the ethical concerns associated with placebo trials when there is a known treatment.
- Inadequate justification for the clinical significance of thresholds related to 3TUG and QMG.
- Potential applicability issues of trial data to the PBS population:
  - Differences in proportions of patients with pLEMS (3% DAPPER trial, 35% DUKE trial) and aLEMS, compared with a typical LEMS population of pLEMS and aLEMS occurring in approximately equal proportions.
  - Uncertainty of the impact of concurrent management and effects of cancer in patients with pLEMS.
  - Limited evidence for effectiveness or safety in paediatric populations, although it is unlikely the evidence base will substantially improve as LEMS is a rare condition for paediatric patients. The PSCR acknowledged the limitations of the evidence based on six paediatric LEMS cases reported in published literature, but considered that safety and efficacy in paediatric patients appeared to be consistent with that observed in adults.
- High risk of bias in the DAPPER trial, and medium risk of bias in the DUKE trial (paragraph 6.14).

6.37 The submission described amifampridine as superior in terms of safety compared to placebo despite evidence of AEs related to amifampridine from the trials and post-marketing surveillance. The PSCR acknowledged that while amifampridine has been used for 15 years on the SAS and therefore has a well-established safety profile, a claim of inferior safety is appropriate. The ESC agreed with the evaluation that the claim of superior safety compared to placebo is not supported.

6.38 The PBAC considered that the submission's claim of superior comparative effectiveness was reasonable, however the magnitude of the effect was uncertain and difficult to determine due to the limitations of the available clinical evidence.

6.39 The PBAC considered that the submission’s claim of superior comparative safety was not supported, and that a claim of inferior safety was appropriate.

**Economic analysis**

6.40 The submission presented a modelled cost-utility analysis based on a randomised trial (DAPPER trial) and data from a sponsor-initiated survey.

6.41 Table 7 presents the key components of the economic model.

**Table 7: Summary of model structure, key inputs and rationale**

Component	Summary
Treatments	Amifampridine vs. placebo
Time horizon	8 years in the model base case vs. 3.5 days in the key trial (DAPPER)
Outcomes	Quality-adjusted life years
Methods used to generate results	Cohort expected value
Health states	Responders Non-responders Dead
Cycle length	4 weeks
Transition probabilities	<u>Response rate from DAPPER trial.</u> Responder definition: No deterioration greater than 30% in 3TUG response. The model assumed that all (100%) patients on amifampridine responded to the treatment.  <u>Treatment discontinuation.</u> The submission assumed all patients will continue to respond to treatment. The submission did not provide a justification for this assumption.  <u>Mortality</u> from Australian life tables.
Health related quality of life	Utilities were sourced from sponsor-initiated surveys on a subset of patients presently treated with amifampridine (N=14). The utilities applied for responders to treatment and non-responders were 0.834 and 0.122, respectively. This indicates a treatment effect of 0.712.
Maximum dose and dosing pattern of amifampridine	Sourced from sponsor-initiated surveys on a subset of patients presently treated with amifampridine (N=14). Initial dose of 2.5 tablets (25 mg) increasing over 60 months (i.e. 66 four-week cycles) to an average maintenance dose of 6.85 tablets (68.5 mg) daily.

Source: Table 3.2, p129 of the submission.

3TUG = Triple Timed Up and Go; N = total participants in group

6.42 The submission presented a cohort expected value analysis. The structure of the economic model is simple which may be appropriate in the context of a rare disease with limited clinical evidence available to inform the model. The model considers three health states (Responders, Non-responders and Dead). Patients remain in the Responder health state or transition into the Non-responder health state as determined by the response rate which remains fixed throughout the entire time horizon. Apart from background mortality, there were no other transitions. Additionally, apart from the cost of amifampridine, no other costs were considered.

- 6.43 The model presented in the submission is different to other published economic evaluations (models reviewed by the Scottish Medicines Consortium (SMC)<sup>e</sup> and Canadian Agency for Drugs and Technologies in Health (CADTH)<sup>f</sup>. There were differences in the method of analysis, comparators, time horizons considered, maximum allowable dose, and utility values applied. Table 8 presents a comparison of the economic models and final recommendations.

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<sup>e</sup> <https://www.scottishmedicines.org.uk/medicines-advice/amifampridine-firdapse-fullsubmission-66010/>

<sup>f</sup> <https://www.cadth.ca/amifampridine>

**Table 8: Comparison of economic model presented in submission**

Component	As presented in submission	Model considered by: <sup>a</sup>	
		SMC	CADTH
Indication	Treatment of LEMS in adults and children aged ≥6 years	Symptomatic treatment of LEMS in adults	Treatment of LEMS patients 6 years of age and older
Comparator	Placebo	Palliative care for patients with LEMS	Best supportive care
Maximum allowable dose	68.5 mg daily (escalated from 25 mg)	60 mg per day	80 mg per day
Time horizon	8 years	1 year	Lifetime (up to 54 years)
Methods used to generate results	Cohort expected value	Information not available	Markov model with 5 health states
Health states	Responders Non-responders Dead	Information not available	Based on severity of QMG score: Asymptomatic (QMG score 0-1); Mild (QMG score 2-7); Moderate (QMG score 8-15); Severe (QMG score from 16-39); and Dead.
Response rate	100%	100%	Information not available
Discontinuation rate	0%	12%	Information not available
Discontinuation rate of non-responders	Not applicable	Discontinue at 3 months	Discontinue at 3 months
Utilities	Sponsor-initiated surveys on subset of patients presently treated with amifampridine (N=14) Responders were assigned a utility value of 0.834 and non-responders 0.122 (gain in utility score of 0.712)	Based on proxy estimates from multiple sclerosis patients (gain in utility score of 0.346)	Based on utility values derived from mean QMG score for each category from a 2011 Cochrane review
Cost of amifampridine (per tablet)	\$ [REDACTED]	£18 (approximately \$33.85 AUD)	CAN\$27.40 (approximately \$29.55 AUD)
Base case results	ICER: \$ [REDACTED] /QALY Incremental cost: \$ [REDACTED] Incremental QALY: 4.24	ICER: £92,267/QALY Incremental cost: £33,124 Incremental QALY: 0.36	ICER: \$453,809/QALY Incremental cost: \$956,144 Incremental QALY: 2.11 QALY
Final recommendation	-	Not recommended due to insufficient justification of treatment cost relative to health benefits and lack of robust economic analysis	Reimburse with conditions that include a price reduction of at least 76%
Other comments	-	Medication evaluated was amifampridine phosphate (Firdapse)	-

<sup>a</sup> Information as extracted from publicly available documents.

Source: Compiled during the evaluation based on Table 3.2, p129 of the submission and information extracted from CADTH Reimbursement Recommendation for Amifampridine (Ruzurgi), 2021 and SMC No. 660/10 Amifampridine 10mg tablet, as phosphate (Firdapse).

AUD = Australian dollars; CADTH = Canadian Agency for Drugs and Technologies in Health; CAN = Canadian dollars; LEMS = Lambert-Eaton myasthenic syndrome; N = total participants in group; QMG= Quantitative Myasthenia Gravis; SMC = Scottish Medicines Consortium.

The redacted values correspond to the following ranges:

<sup>1</sup> \$115,000 to < \$135,000

- 6.44 The submission economic model relied on (i) the primary efficacy endpoint (a greater than 30% deterioration in 3TUG response) in the DAPPER trial; (ii) patient-reported HRQoL outcomes; and (iii) maximum amifampridine dose from a survey conducted by the sponsor on Australian LEMS patients. The key issues with the model were:
- There is high risk of sampling bias given the withdrawal study design of the DAPPER trial (paragraph 6.17). The model reflected LEMS patients who were already responding to treatment and did not adequately capture treatment naïve patients who may respond differently to amifampridine. Using the response rate from the DAPPER trial in the model may overstate the effectiveness of amifampridine.
  - Utility data from the sponsor-initiated survey was based on a subset of patients currently treated with amifampridine (N=14). Individual (de-identified) patient responses were provided as an attachment to the submission, however limited details of the methodology of the survey were provided (paragraph 6.45). There was no information on the criteria for patient selection aside from all patients being currently on treatment with amifampridine.
  - The validity of utility scores was highly uncertain (paragraph 6.45).
- 6.45 Utility values for HRQoL and amifampridine dosing data used to inform the economic model were obtained from a sponsor-initiated patient survey. The survey (which included questions on duration of diagnosis with LEMS and treatment with amifampridine, current dose of amifampridine, occupation and living arrangements) was sent out to 17 LEMS patients (currently treated with amifampridine) in Australia. The survey included the EQ-5D-5L to measure patients' retrospectively recalled health state prior to receiving treatment with amifampridine and their present utility whilst receiving treatment with amifampridine. Fourteen patients (82%) completed the EQ-5D questionnaires and 11 (65%) provided data on their current dose. The key issues with the patient survey were:
- The submission did not provide information on the criteria for patient selection aside from all patients being currently on treatment with amifampridine and no patient characteristics such as age, sex and concomitant medications were reported.
  - Although LEMS is a rare disease, the sample size appears small (<27%) relative to the number of patients the submission claimed to be currently treated with amifampridine in Australia (between 51 and 55 based on numbers used estimate the financial implications).
  - The duration of treatment from the survey sample of patients ranged from 0.25 to 16 years. There is high risk of recall bias for those who were asked to retrospectively report their HRQoL prior to treatment with amifampridine.

- As these patients were already on amifampridine, they were likely to be representative of a subset of the proposed PBS population; i.e., grandfathered patients already accessing amifampridine through SAS. It may have not adequately accounted for patients that would initiate amifampridine as a result of PBS listing or patients who currently do not receive it due to restricted access.
- 6.46 The utilities applied in the model for responders to treatment and non-responders were 0.834 and 0.122, respectively. The ICER was most sensitive to the utility values applied, particularly for the non-responder health state. While the PSCR stated that the utility values derived from the 14 LEMS patients was the best available evidence for the Australian LEMS population, the ESC considered that the validity of the utility values is highly uncertain. The ESC noted that utilities reported in Harms et al (2012)<sup>g</sup> for 12 German LEMS patients provide a reasonable alternative utility value (0.31) for non-responders.
- 6.47 The submission assumed an initial dose of 2.5 tablets (25 mg) increasing over 60 months to an average maintenance dose of 6.85 tablets (68.5 mg) daily. The escalation period of 60 months (66 four-week cycles) appears to be inappropriate, as amifampridine is used for symptomatic treatment and, based on the design of the DAPPER trial, treatment is shown to be effective soon after dosing. Further, although there was an escalation of the drug to average maintenance dose by 60 months, the full impact on quality of life for responders was applied from Day 1. The ESC noted the assumption of immediate improvement in HRQoL favours amifampridine.
- 6.48 The application of mortality rates from the Australian life tables may not adequately represent pLEMS (typically associated with SCLC and expected to represent 50% of LEMS population). This is inconsistent with the PBS proposed population of patients with LEMS (including aLEMS and pLEMS). Different utilities and mortality rates may apply to pLEMS, however there is a lack of data to inform a separate model for this sub-population. The ESC acknowledged the lack of mortality data to inform the pLEMS population and that available literature indicates that patients with pLEMS appear to have improved survival over non-LEMS SCLC patients, however it considered the survival of these patients is unlikely to be similar to the general population.
- 6.49 The submission did not include costs for the management of AEs. There is evidence of AEs relating to amifampridine use from trials and post-marketing surveillance data (e.g., treatment related AEs were reported in 68 (42%) of patients in the RPV162 group [paragraph 6.26]) and 48 patients (30%) in the RPV162 group had their amifampridine dose adjusted or discontinued due to an AE. More than half of the Special Populations group adjusted or discontinued amifampridine due to an AE (paragraph 6.27).

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<sup>g</sup> Lutz Harms, Jörn-Peter Sieb, Angela E. Williams, Ryan Graham, Rita Shlaen, Volker Claus & Carmen Pfiffner (2012) Long-term disease history, clinical symptoms, health status, and healthcare utilization in patients suffering from Lambert Eaton myasthenic syndrome: Results of a patient interview survey in Germany, *Journal of Medical Economics*, 15:3, 521-530, DOI: 10.3111/13696998.2012.660897

Amifampridine can cause serious AEs such as seizures and cardiac-related events (paragraph 6.29). The ESC agreed with the evaluation that not accounting for potential AEs favours amifampridine. The ESC noted that the model structure was not designed to allow disutility and cost accrual associated with AEs to be estimated without significant reworking.

- 6.50 The submission assumed that all patients on amifampridine would continue to be on the medication over the entire time horizon, thus assuming a discontinuing rate of 0%. This is not appropriate as the long-term effectiveness and safety of amifampridine is unknown and there is evidence of discontinuations due to AEs (paragraph 6.51). Not accounting for potential discontinuation following treatment favours amifampridine.
- 6.51 The model applied a fixed 100% response rate across the entire 8-year time horizon, based on 3TUG results from the DAPPER trial. It is possible that some patients will lose their response or discontinue due to AEs, consistent with the withdrawal of 1 patient from the DUKE trial (paragraph 6.25) and patients in both the Special Populations and RPV162 groups adjusting or discontinuing amifampridine (paragraph 6.27). A loss of response in the DAPPER trial may not have been captured due to the withdrawal study design. Available data suggested that between 11–22% of patients treated with amifampridine may discontinue due to AEs within the first year of treatment (paragraph 6.25). An 89% fixed response rate (assuming 11% of patients withdrew) was tested in a sensitivity analysis and results were sensitive to this change, with the ICER increasing from \$115,000 to < \$135,000 per QALY (base case corrected during evaluation) to \$135,000 to < \$155,000 per QALY (Table 11).
- 6.52 For patients in the placebo arm, a response rate of 10% was applied in the base case. This rate could not be verified, and a rate of 27.8% as per the DAPPER trial should have been used instead if it is accepted that the model is informed by the outcome of >30% deterioration in 3TUG test as reported for the DAPPER trial (i.e. 72.2% of patients in the taper-to-placebo arm, Table 4). Adjusting the placebo response rate to 27.8% increased the ICER to \$135,000 to < \$155,000 per QALY gained from \$115,000 to < \$135,000 per QALY (base case corrected during evaluation) (Table 11).
- 6.53 The submission claimed that patients on treatment with amifampridine will have a 50% reduction of IVIg use, but did not include this reduction in the economic model. This claim could not be verified. There is uncertainty whether and how IVIg could be displaced or may be added to therapy.
- 6.54 Patients with LEMS are likely to be treated with concurrent medications in addition to amifampridine, such as pyridostigmine, prednisolone, or azathioprine. For example, 81.3% of patients in the DAPPER trial were concurrently on pyridostigmine. However, it is uncertain if treatment with amifampridine would result in an increase or decrease in use of these concurrent medications. These were not considered in the economic model and it may be inappropriate to exclude them. The ESC considered that further information on potential changes to IVIg or other concurrent therapies would be informative for interpretation of the economic model. The pre-PBAC response stated

that reduction in use of other treatments, notably IVIg, was considered, but not incorporated in the modelled economic evaluation due to lack of reliable data.

6.55 Table 9 summarises the key drivers of the model.

**Table 9: Key drivers of the model**

Description	Method/Value	Impact Base case: \$ [redacted] /QALY gained (corrected by evaluator)
Utilities	Utilities sourced from sponsor-initiated surveys on subset of patients presently treated with amifampridine (N=14). Utilities applied for responders to treatment and non-responders were 0.834 and 0.122, respectively. Utility applied to non-responders was highly uncertain because there is a high risk of recall bias. Further, the implied utility difference of 0.711 is large and higher than the utility difference between responders and non-responders used in the Scottish Medicines Consortium (SMC) model (0.346) see Table 8 for further details.	High, favours amifampridine. Increasing non-responder utility to 0.31 increased the ICER to \$ [redacted] <sup>2</sup> per QALY gained.
Maximum amifampridine dose applied	Sourced from sponsor-initiated surveys on subset of patients presently treated with amifampridine (N=14). Initial dose of 2.5 tablets (25 mg) increasing over 60 months (i.e. 66 four-week cycles) to an average maintenance dose of 6.85 tablets (68.5 mg) daily. Amifampridine is used for symptomatic treatment and doses can vary depending on the needs of the patient. A maximum dose of 100 mg is possible. Higher doses would result in an increased ICER.	High, favours amifampridine. Increasing to maximum dose of 10 tablets (10 mg) daily with no dose escalation increased the ICER to \$ [redacted] <sup>2</sup> per QALY gained.
Response rate	The model applied a 100% response rate for patients on amifampridine based on results from the DAPPER trial.  For patients in the placebo arm, a response rate of 10% was applied. This rate could not be verified. A response rate of 27.8% for the placebo arm (DAPPER trial) should have been used instead.	Moderate, favours amifampridine. Decreasing amifampridine response rate to 89% increased ICER to \$ [redacted] <sup>3</sup> per QALY gained.  Moderate, favours amifampridine. Correcting placebo response rate to 27.8% increased ICER to \$ [redacted] <sup>3</sup> per QALY gained.

Source: Tables 3.14, pp148-149 of the submission and from sensitivity analyses conducted during the evaluation.  
ICER = incremental cost-effectiveness ratio; N = total participants in group; QALY = quality-adjusted life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$115,000 to < \$135,000

<sup>2</sup> \$155,000 to < \$255,000

<sup>3</sup> \$135,000 to < \$155,000

6.56 The submission did not provide a justification for not presenting a stepped economic evaluation. A trial-based evaluation based on cost and outcomes (>30% deterioration in 3TUG test) from the DAPPER trial was conducted during the evaluation.

6.57 Table 10 presents the results of the economic evaluation.

Table 10: Results of the economic evaluation

	Amifampridine	Placebo	Increment
<b>Trial-based evaluation; over 6 days; drug costs only; outcome = experiencing &lt;30% deterioration, no change or improvement in 3TUG test<sup>a</sup></b>			
Total cost (\$)	██████ <sup>b</sup>	\$0	██████
% responder	100	27.8	72.7
<b>Incremental cost per extra responder</b>			██████ <sup>1</sup>
<b>Base case results as presented in the submission</b>			
Costs (\$)	██████ <sup>b</sup>	\$0	██████ <sup>b</sup>
QALYs	5.520	1.281	4.239
<b>Incremental cost per QALY gained</b>			██████ <sup>b, 2</sup>
<b>Base case results (corrected during evaluation)</b>			
Costs (\$)	██████	\$0	██████
QALYs	5.502	1.277	4.226
<b>Incremental cost per QALY gained</b>			██████ <sup>2</sup>

Source: Table 3.12, p146 of the submission.

QALY = quality adjusted life year; 3TUG = Triple Timed Up and Go.

<sup>a</sup> This outcome was inverted to ease interpretation. It still represents the same numbers for outcome of >30% deterioration in 3TUG test.

<sup>b</sup> As presented in submission based on DPMQ of \$██████ for a maximum quantity of 200 amifampridine tablets, and a DPMQ price of \$██████ per tablet. The correct DPMQ should be \$██████ and cost per tablet is \$██████ at the DPMQ price. This correction resulted in a very small change to the ICER and favours the placebo arm – ICER changed from base case of \$115,000 to < \$135,000 per QALY to \$115,000 to < \$135,000 per QALY.

The redacted values correspond to the following ranges:

<sup>1</sup> 0 to < \$5,000

<sup>2</sup> \$115,000 to < \$135,000

#### 6.58 The results should be considered with caution because:

- There is large uncertainty in the utility values applied in the model, particularly for the non-responder health state. There is high risk of recall bias and uncertainty in eliciting retrospective HRQoL (utility values) for the non-responder health state. This was lower than the average utility (0.31) of LEMS patients reported in the study reported by Harms et al. Further, a mean utility value of 0.834 was applied for treatment responders in the economic model, which is higher than the maximum utility value (0.77) reported by Harms et al over the duration of their study (7 days). The ICER was very sensitive to the utility values applied (Table 9).
- The modelled total QALY gain presented in the submission is considerably larger than gains seen in the CADTH<sup>h</sup> and SMC<sup>i</sup> models (paragraph 6.43). The base case of the SMC model considered a time horizon of 1 year, producing a total QALY gain of 0.36. This compares with 0.671 QALYs gained at 1 year using the economic model presented by the submission. The base case of the CADTH model produced a total QALY gain of 2.107 with a lifetime horizon, compared to 9.585 QALYs gained using the economic model presented by the submission with a lifetime horizon also applied.

<sup>h</sup> <https://www.cadth.ca/amifampridine>

<sup>i</sup> <https://www.scottishmedicines.org.uk/medicines-advice/amifampridine-firdapse-fullsubmission-66010/>

6.59 The results of key univariate sensitivity analyses are summarised in Table 11.

**Table 11: Univariate sensitivity analyses**

	Analyses	Incremental cost (\$)	Incremental QALY	ICER	Change from corrected base case ICER
	Base case (presented in submission)	████████	4.239	████████ <sup>1</sup>	
	Base case (with corrections) <sup>a</sup>	████████	4.226	████████ <sup>1</sup>	
<b>(1)</b>	<b>Placebo cohort responder rate</b>				
	Applied 27.8% as per DAPPER trial	████████	3.390	████████ <sup>2</sup>	25%
<b>(2)</b>	<b>Utility values</b>				
	Applying 0.77 (maximum utility of LEMS patients from Harms et al) to responders	████████	3.847	████████ <sup>1</sup>	10%
	Applying 0.31 (average utility of LEMS patients from Harms et al) to non-responders	████████	3.111	████████ <sup>3</sup>	36%
	Applying utility gain of 0.346 as considered by the SMC <sup>b</sup>	████████	2.055	████████ <sup>3</sup>	106%
<b>(3)</b>	<b>Dosing</b>				
	No dose escalation – dose of 7.5 tablets daily (based on mean daily dose in the DAPPER trial)	████████	4.226	████████ <sup>3</sup>	42%
	Dose escalation from 2.5 to 6.85 within a 3-month time frame (remains constant thereafter) <sup>c</sup>	████████	4.226	████████ <sup>3</sup>	27%
	Dose escalation from 2.5 to 10 (maximum dose from sponsor-initiated survey) within a 3-month time frame (remains constant thereafter) <sup>c</sup>	████████	4.226	████████ <sup>3</sup>	85%
<b>(4)</b>	<b>Discontinuation rate</b>				
	Responder rate of 89% (proxy for assumed discontinuation rate of 11%)	████████	3.709	████████ <sup>2</sup>	14%
	Responder rate of 78% (proxy for assumed discontinuation rate of 22%)	████████	3.193	████████ <sup>3</sup>	32%

Shading shows the components of the re-specified base case in Table 12.

<sup>a</sup> Corrections applied were described in Section 3.1 of the commentary, which included calculation errors related to cycle length, survival probabilities, discount rate, and the calculation of discounted costs and outcomes.

<sup>b</sup> Scottish Medicines Consortium (Amifampridine 10 mg tablet, as phosphate (Firdapse®) SMC No.(660/10), August 2012)

<sup>c</sup> Escalation time frame similar to CADTH model assumption

Source: Compiled during the evaluation using evaluator corrected models

CADTH = Canadian Agency for Drugs and Technologies in Health; ICER = incremental cost-effectiveness ratio; LEMS = Lambert-Eaton myasthenic syndrome; QALY = quality-adjusted life year; SMC = Scottish Medicines Consortium

The redacted values correspond to the following ranges:

<sup>1</sup> \$115,000 to < \$135,000

<sup>2</sup> \$135,000 to < \$155,000

<sup>3</sup> \$155,000 to < \$255,000

6.60 The ESC noted the key parameters explored in the univariate sensitivity analyses (Table 11) and recommended a revised base case as set out in Table 12 below. The proposed changes for the respecified base case include:

- (1) Change placebo response rate to 27.8%
- (2) Apply alternative utility value of 0.31 to the non-responder health state (Harms, 2012)
- (3) Apply dose escalation from 2.5 to 6.85 tablets per day within a 3-month time frame

(4) Apply responder rate of 89% (proxy for assumed discontinuation rate of 11%).

6.61 The stepped results for each of these changes are presented in Table 12. The application of these proposed changes produced an ICER of \$311,546 per QALY gained and this was considered to be a more appropriate base case.

**Table 12: Stepped approach for the ESC respecified base case**

	Analyses	Incremental cost (\$)	Incremental QALY	ICER	% change from base case ICER
	<b>Base case (presented in submission)</b>	██████████	4.239	██████████ <sup>1</sup>	
	Base case (with corrections during evaluation) <sup>a</sup>	██████████	4.226	██████████ <sup>1</sup>	
(1)	Placebo cohort responder rate at 27.8%	██████████	3.390	██████████ <sup>2</sup>	25%
(2)	Step 1 + Applying 0.31 (average utility of LEMS patients from Harms et al) to non-responders	██████████	2.495	██████████ <sup>3</sup>	69%
(3)	Step 2 + Dose escalation from 2.5 to 6.85 within a 3-month time frame (remains constant thereafter) <sup>b</sup>	██████████	2.495	██████████ <sup>4</sup>	115%
(4)	Step 3 + Responder rate of 89% (proxy for assumed discontinuation rate of 11%)	██████████	2.115	██████████ <sup>4</sup>	154%
	<b>Proposed respecified base case applying all parameters (with submission price)</b>	██████████	<b>2.115</b>	██████████ <sup>4</sup>	<b>154%</b>

<sup>a</sup> Corrections applied were described in Section 3.1 of the commentary and are applied to all steps

<sup>b</sup> Escalation time frame similar to CADTH model assumption

Source: Compiled during the evaluation evaluator corrected models

CADTH = Canadian Agency for Drugs and Technologies in Health; ICER = incremental cost-effectiveness ratio; LEMS = Lambert-Eaton myasthenic syndrome; QALY = quality-adjusted life year; SMC = Scottish Medicines Consortium

The redacted values correspond to the following ranges:

<sup>1</sup> \$115,000 to < \$135,000

<sup>2</sup> \$135,000 to < \$155,000

<sup>3</sup> \$155,000 to < \$255,000

<sup>4</sup> \$255,000 to < \$355,000

6.62 The pre-PBAC response proposed an alternative base case as set out in Table 13 below. Incorporating these changes to the modelled economic evaluation resulted in an updated ICER of \$155,000 to < \$255,000 per QALY gained. The pre-PBAC response proposed a price reduction of 21% to achieve an ICER equivalent to the submission (\$115,000 to < \$135,000 per QALY gained - base case corrected during evaluation). The proposed changes for the pre-PBAC response base case include:

- (1) Apply a placebo response rate of 18%;
- (2) Apply utility value of 0.122 to the non-responder health state;

- (3) Apply dose escalation from 2.5 to 6.85 tablets per day over 66 cycles;
- (4) Apply responder rate of 89% (proxy for assumed discontinuation rate of 11%).

**Table 13: Comparison of inputs as discussed in pre-PBAC response**

	Base Case	ESC re-specification	Pre-PBAC response	Consideration
Utility values – non-responders	0.122	0.31	0.122	The pre-PBAC response acknowledged the limitations of the data sample informing the model, but stated that the 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. The PBAC considered the utility gain associated with treatment remained uncertain.
Response rate – on treatment	100%	89%	89%	The pre-PBAC response accepted the ESC Advice with respect to applying a responder rate of 89% (proxy for assumed discontinuation rate of 11%), which the PBAC considered was reasonable.
Response rate - placebo	10%	27.8%	18%	The pre-PBAC response proposed that a placebo response rate of 18% would be more appropriate, and cited a supportive analysis from the DAPPER CSR in which the 3TUG result was treated as a continuous response, as compared with the primary analysis reported in the submission which was based on a “point in time” as stipulated by the study protocol. The PBAC agreed with ESC that a placebo response rate of 27.8% reflected the primary analysis of the DAPPER study (paragraph 6.52), notwithstanding that DAPPER was a withdrawal study and there was limited evidence to determine a more accurate estimate of the incremental benefit.
Dose escalation	Over 60 months (66 cycles)	Over 3 months (4 cycles)	Over 60 months (66 cycles)	The pre-PBAC response (2) maintained that dose escalation occurs gradually in clinical practice, and stated that the escalation period in the submission was based on the results of a patient survey. The PBAC noted that the model assumed that benefits of amifampridine treatment would commence immediately. The PBAC agreed with ESC that a 3 month escalation period would be appropriate, and given the trial data, should not be more than 6 months.

Source: Modified from Table 1, Pre-PBAC response.

6.63 While the PBAC raised several concerns with the updated base case proposed in the pre-PBAC response, as discussed in Table 13, it considered it to be unlikely that further data would become available to reduce the uncertainty in the modelled inputs, given the primary clinical evidence for amifampridine is limited to two very small RCTs (n=32 and n=26), and the drug has been used in clinical practice for many years.

## Drug cost/patient/year

Table 14: Drug cost per patient for amifampridine

	Trial dose and duration	Model	Financial estimates
Mean dose per day	67.85 mg	55 mg <sup>b</sup>	60.9 mg
Mean duration	6 days <sup>a</sup>	Daily for 8 years, no discontinuation or dose change	Daily, no discontinuation or dose change
Cost/patient/month (\$)	<i>██████████</i> <sup>c</sup>	<i>██████████</i> <sup>c</sup>	<i>██████████</i> <sup>c</sup>
Cost/patient/year (\$)	<i>██████████</i> <sup>c</sup>	<i>██████████</i> <sup>c</sup>	<i>██████████</i> <sup>c</sup>

Source: Table 26, pp 156-157 of the trial report, Section 3 workbook, sheet 3a of the utilisation-and-cost-model. Italicised values have been calculated.

<sup>a</sup> Due to nature of the study design (drug withdrawal study)

<sup>b</sup> Cumulative prescribed dose during treatment period divided by treatment duration (105 cycles)

<sup>c</sup> DPMQ corrected during the evaluation

## Estimated PBS usage & financial implications

6.64 This submission was considered by DUSC. The submission presented an analysis based on historical patient sales data to inform on the current patients on hospital/private funded amifampridine treatment to estimate the financial implications to the Australian Government. Given that LEMS is a rare disease and that there is limited data available on the Australian LEMS population, the approach applied is reasonable.

6.65 Table 15 summarises the key inputs and issues for financial estimates.

**Table 15: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
Incident patients	This was not provided in the submission and assumed to be 0.	The submission assumed all LEMS patients were already on amifampridine treatment (all patients would be grandfathered). This is not appropriate and may be an underestimate. Current treatment is not universally subsidised thus limiting access. Although LEMS is a rare condition, new patients will be diagnosed over time.
Number of patients currently treated with amifampridine	Ranging from 51 (Year 1) to 55 (Year 6). Estimated based on historical sales data for amifampridine use under SAS and average dose estimated from sponsor-initiated survey (Patients = Units sold / Average dose)	These were lower than estimates from global prevalence literature (ranging between 44 and 269 patients). The upper estimate is based on reported crude prevalence of 10.9 per million from Abenroth et al (2017). The prevalence has a wide range and remains very uncertain.
Grandfathered patients	All LEMS patients. Source: Assumption	The submission assumed that all LEMS patients are currently already on amifampridine therefore all patients would be grandfathered. This aligns with the assumption that 100% will meet proposed restriction and 100% will take up treatment as applied in the economic model. This appears reasonable.
Dose	An average dose of 6.09 tablets (60.9mg) daily based on sponsor-initiated survey.	The evidence base used to estimate the average daily dose was based on small patient numbers (N=11) through a survey initiated by the sponsor. This input was applied in two key calculations – (i) To estimate the number of LEMS patients from historical sales data; and (ii) To calculate the expected cost and scripts to inform financial estimates. The doses reported from patients' responses in the survey ranged from 2.5 (25 mg) to 10 (100 mg) tablets daily. The mean daily dose of amifampridine reported at randomisation in the DAPPER trial was 75.7 mg, range 30-100 mg. This is also inconsistent with the maximum dose applied in the economic model in Section 3. The financial estimates were highly sensitive to this change.

Source: Compiled during the evaluation based on information presented in p151-153 of the submission.

LEMS = Lambert-Eaton myasthenic syndrome; SAS = Special Access Scheme

6.66 The submission stated that there is no PBS listed medicines that are expected to be substituted/replaced by the listing of amifampridine. This is uncertain as the following PBS-listed medicines may be considered alternative therapies: pyridostigmine, azathioprine, mycophenolate mofetil, ciclosporin, and prednisolone. It is uncertain if treatment with amifampridine would result in an increase or decrease in use of these

concurrent medications. These medications are PBS listed and can be used to manage LEMS symptoms as these are general schedule medications with no authority required. These were also not considered in the economic model in Section 3.

- 6.67 The submission indicated that patients on treatment with amifampridine have a 50% reduction of IVIg use, but did not include this reduction in IVIg use in the economic model or financial implication estimates. This claim could not be verified. Data on IVIg use from the National Blood Authority showed that IVIg was supplied to 24 patients in 2017/2018 as additional therapy for LEMS where symptomatic therapy is insufficient. There is uncertainty whether and how IVIg could be displaced or may be added to therapy.
- 6.68 The estimated financial implications of listing amifampridine for the treatment of LEMS are presented in Table 16.

**Table 16: Estimated use 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>a</sup>	■ <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>						
Cost to PBS/RPBS less copayments	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>
Net cost to PBS/RPBS	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>
Net cost to PBS/RPBS (corrected DPMQ) <sup>b</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>

Source: Table 4.6, p153 of the submission

DPMQ = dispensed price for maximum quantity

<sup>a</sup> Assuming 11.12 scripts per year as estimated by the submission.

<sup>b</sup> Calculated during the evaluation using the corrected DPMQ

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

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

- 6.69 The total cost to the PBS/RPBS of listing amifampridine was estimated to be \$0 to < \$10 million in Year 6, and a total of \$20 million to < \$30 million in the first 6 years of listing.
- 6.70 The net cost to the PBS/RPBS may be underestimated because:
- Current patient numbers on amifampridine appears to be lower than global prevalence estimates from literature (e.g., estimates from global prevalence literature (Abenroth, 2017) report a crude prevalence of 10.9 million, translating to about 269 patients in Australia
  - Estimated patient numbers reflect LEMS patients that are already on amifampridine treatment (grandfathered from SAS access), therefore omits possible uptake by new LEMS patients

- There is potential for use outside the requested restriction, such as disorders caused by paraneoplastic syndrome, which covers a range of conditions including LEMS
  - Costs related to management of AEs from amifampridine use were not considered.
- 6.71 The financial estimates were most sensitive to the underlying number of patients expected to be on amifampridine and the expected dose which will drive the number of prescriptions and cost.
- 6.72 The submission indicated that all LEMS patients are currently already on amifampridine through the Special Assess Scheme (SAS) and would be grandfathered. The current financial estimates only reflect grandfathered patients and have not accounted for uptake by new LEMS patients, i.e. the submission assumes that PBS listing will have no impact on access to amifampridine because all patients currently have access via SAS.
- 6.73 The DUSC noted that there is a risk that the SAS application numbers highlight an equity issue due to regional variability in accessing the SAS scheme, and also pricing arrangements between patients and hospitals that may impact affordability. In addition, the SAS data would not include patients who are unable to access the SAS scheme but would be able to access amifampridine if listed on the PBS.
- 6.74 The results of the sensitivity analyses are presented in Table 17. The financial estimates increased significantly up to \$100 million to < \$200 million over 6 years (increased by 426% from base case) when the prevalence of LEMS was increased substantially to 10.9 per million.

**Table 17: Results of the sensitivity analyses**

Year	2022	2023	2024	2025	2026	2027
<b>Net cost to PBS/RPBS</b>						
Base case	1	1	1	1	1	1
<b>Number of patients on amifampridine</b>						
Prevalence of LEMS = 1 in 291,650 <sup>a</sup>	1	1	1	1	1	1
Prevalence of LEMS = 10.9 per million <sup>b</sup>	2	2	2	2	2	2
<b>Average dose in practice</b>						
10 tablets daily <sup>c</sup>	1	1	1	1	1	1

\* These estimates were based on a DPMQ of \$8,215.30 as presented in the submission.

Source: Tables 4.9 to 4.14, p157-159 of the submission and calculated during evaluation

<sup>a</sup> Based on mid-point estimate from Titulaer (2013); patient numbers range from 85 to 91

<sup>b</sup> Based on crude prevalence reported in Abenroth (2017); patient numbers range from 269 to 290

<sup>c</sup> Maximum dose allowed

The redacted values correspond to the following ranges:

<sup>1</sup> \$0 to < \$10 million

<sup>2</sup> \$20 million to < \$30 million

### **Financial Management – Risk Sharing Arrangements**

- 6.75 No risk sharing arrangements were proposed in the submission, however the submission indicated a willingness to discuss to ensure the listing of amifampridine in a timely manner.

### **Quality Use of Medicines**

- 6.76 No quality use of medicines (QUM) information was provided in the submission.
- 6.77 The DUSC agreed with the commentary that education of health practitioners would be advisable, particularly relating to optimising patient doses.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of amifampridine for the treatment of Lambert-Eaton myasthenic syndrome in adults and children aged 6 years and above. The PBAC noted the high clinical need for effective treatments for these patients. The PBAC considered the clinical evidence informing the cost-effectiveness evaluation had a high risk of bias, and that the incremental benefit was uncertain due to limitations of the available clinical evidence. The PBAC considered the ICER was unacceptably high and uncertain at the proposed price.
- 7.2 The PBAC noted the input from individuals, health care professionals and organisations which highlighted the positive impact that amifampridine has on muscle strength and quality of life. In addition, the PBAC noted comments supporting the proposed PBS listing of amifampridine on the basis this would improve access for patients compared with current SAS arrangements.
- 7.3 The PBAC considered that the requested written authority listing for amifampridine was not required, and that in the context of amifampridine being prescribed by a neurologist or immunologist, a telephone/online PBS authority would be appropriate.
- 7.4 The PBAC considered that the nomination of placebo ('standard medical management') as the main comparator was appropriate.
- 7.5 The PBAC noted that the submission was based on two small randomised, double-blind, placebo-controlled, trials: DAPPER (a randomised, double-blind, placebo-controlled, withdrawal study in patients who had been on a stable dose of amifampridine for at least three continuous months, N=32) and DUKE (a randomised, double-blind, placebo-controlled study in treatment-naïve patients, N=26). The PBAC noted that both randomised trials had a substantial risk of bias (high risk of bias for DAPPER due to eligible patients having successfully responded to amifampridine before randomisation, and medium risk of bias for DUKE due to a lack of information provided in the submission and publication).

- 7.6 The PBAC noted the results of the DAPPER and DUKE trials which demonstrated the efficacy of amifampridine compared with placebo. In the DAPPER trial, 72% of patients (13/18) randomised to the taper-to-placebo arm experienced a greater than 30% deterioration in the final 3TUG test, while none of the patients randomised to amifampridine experienced this deterioration ( $p < 0.05$ ). In the DUKE trial, the QMG score improved at least two points in 58% of patients (7/12) randomised to amifampridine, but none of the patients taking placebo ( $p < 0.05$ ). The PBAC noted the conclusion of the TGA Clinical Evaluation Report which stated that the QMG results of the DUKE trial were statistically significant and clinically relevant in patients treated with amifampridine.
- 7.7 The PBAC noted the evidence of adverse events related to amifampridine from clinical trials and post-marketing surveillance. The PBAC noted that amifampridine is reported to have a narrow therapeutic index, and that severe adverse events have been reported to be related to amifampridine including convulsions, loss of consciousness, tremor, atrial fibrillation, anxiety, chest pain, fall, and accidental overdose.
- 7.8 The PBAC considered 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.
- 7.9 The submission presented a modelled cost-utility analysis based on the DAPPER trial and data from a sponsor-initiated survey. The PBAC considered there is inherent uncertainty in the modelled estimates due to lack of available data on the response rates and long term quality of life and mortality outcomes of the proposed population.
- 7.10 The PBAC noted the updated base case proposed in the pre-PBAC response, which increased the ICER to \$155,000 to  $< \$255,000$  per QALY gained. The PBAC also noted the price reduction of 21% proposed in the pre-PBAC response, which would result in the same ICER as submitted ( $\$115,000$  to  $< \$135,000$  per QALY gained – base case corrected during evaluation). The PBAC reviewed the rationale for the updated base case proposed in the pre-PBAC response and considered that, in the context of the limited clinical evidence available, it was reasonable to accept the inputs as specified in the pre-PBAC response, however the PBAC considered that the presented ICER of  $\$115,000$  to  $< \$135,000$  per QALY gained was high and uncertain. The PBAC considered that the cost-effectiveness of amifampridine would be considered acceptable if the pre-PBAC response assumptions were used, and the price was reduced to reflect an ICER less than  $\$85,000$ /QALY.
- 7.11 The PBAC noted that the financial implications analysis was based on historical patient sales data. The PBAC considered that given that LEMS is a rare disease and that there is limited data available on the Australian LEMS population, the approach applied was reasonable.
- 7.12 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for amifampridine using the early re-entry pathway. If the sponsor

accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.

- A price reduction to achieve an ICER of less than \$85,000/QALY gained based on the scenario outlined in paragraph 7.10.
- Recalculation of the financial implications using the revised amifampridine price.

The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.13 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Not recommended

## **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.