

CADTH Reimbursement Recommendation

# Amifampridine Phosphate (Firdapse)

**Indication:** For the treatment of Lambert-Eaton myasthenic syndrome in adults

**Sponsor:** KYE Pharmaceuticals Inc.

**Final recommendation:** Reimburse with conditions

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## What Is the CADTH Reimbursement Recommendation for Firdapse?

CADTH recommends that Firdapse be reimbursed by public drug plans for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) only if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Firdapse should only be covered to treat patients who are 18 years of age and older and have LEMS.

### What Are the Conditions for Reimbursement?

Firdapse should only be reimbursed if the patient is under the care of a neurologist with expertise in managing LEMS and if the price of Firdapse is reduced.

### Why Did CADTH Make This Recommendation?

- In 2 clinical trials, patients with LEMS who stayed on treatment with Firdapse had less disability progression than patients who stopped Firdapse.
- Based on CADTH's assessment of the health economic evidence, Firdapse does not represent good value to the health care system at the public list price. The committee determined that a price reduction is required.
- Based on public list prices, Firdapse is estimated to cost the public drug plans approximately \$8 million over the next 3 years. However, the actual budget impact is uncertain.

## Additional Information

### What is LEMS?

LEMS is a rare disease where the immune system attacks the body's own connections between nerves and muscles. Symptoms include muscle weakness in the legs and hips and reduced reflexes. As LEMS progresses, patients may experience weakness in the arms, swallowing difficulties, slurred speech, neck weakness, double vision, and droopy eyes. It can occur in association with a cancer diagnosis or appear on its own.

### Unmet Needs in LEMS

Amifampridine, the active ingredient in Firdapse, is considered the standard of care in LEMS. However, it has only been available through Health Canada's Special Access Programme. Thus, lack of access to treatment has been the major limitation for patients with LEMS in Canada.

### How Much Does Firdapse Cost?

At the public list price, treatment with Firdapse is expected to cost approximately \$51,993 per patient per year.

## Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that amifampridine phosphate be reimbursed for the symptomatic treatment of LEMS only if the conditions listed in [Table 1](#) are met.

## Rationale for the Recommendation

Two phase III, randomized, double-blind, placebo-controlled studies, LMS-002 (N = 38) and LMS-003 (N = 26), demonstrated that continuous treatment of patients with amifampridine phosphate was associated with a reduction in disability progression compared with patients for whom amifampridine phosphate was replaced with placebo. In the LMS-002 study, patients who discontinued amifampridine phosphate treatment reported a statistically significant disease progression according to the coprimary end point of difference in Quantitative Myasthenia Gravis (QMG) least squares (LS) means of -1.7 (95% confidence interval [CI]), -3.4 to -0.0; P = 0.0452), compared with patients who continued to receive the drug. Similarly, patients in the LMS-003 trial who discontinued amifampridine phosphate reported both a statistically and clinically significant QMG LS means difference of -6.54 (95% CI, -9.78 to -3.29; P = 0.0004).

Patients and the clinical expert consulted by CADTH identified a need for treatments that can improve activities of daily living and health-related quality of life (HRQoL). The effect of amifampridine on HRQoL and productivity was not evaluated in the LMS-002 and LMS-003 studies; thus, remains unknown.

The pharmacoeconomic model submitted by the sponsor compared the cost of amifampridine phosphate to amifampridine base. Using the sponsor-submitted price for amifampridine phosphate and publicly listed prices for all other drug costs, amifampridine phosphate was less costly compared with amifampridine base and considered similarly effective.

The cost-effectiveness of amifampridine phosphate compared to best supportive care is unknown, due to a lack of comparative evidence. CADTH estimated that a price reduction would be needed to achieve a willingness-to-pay threshold of \$50,000 per quality-adjusted life-year.

**Table 1: Reimbursement Conditions and Reasons**

Reimbursement condition	Reason	Implementation guidance
<b>Initiation</b>		
1. Amifampridine phosphate should be reimbursed when initiated in adult patients with LEMS who are 18 years of age and older.	The LMS-002 and LMS-003 trials demonstrated a clinical benefit in adult patients with LEMS. The Health Canada indication specifies that amifampridine is only to be used in patients 18 years of age and older.	—

Reimbursement condition	Reason	Implementation guidance
<b>Renewal</b>		
2. Patients should be assessed for a response to treatment within 3 months of initiating amifampridine using the 3TUG test (> 30% improvement compared to baseline or continued response).	Although studies LMS-002 and LMS-003 used QMG score as their primary outcome, clinical experts noted that the 3TUG score is the preferred outcome measure used in clinical practice and that titration to the optimal effective dose requires between 2 and 3 months.	<p>The 3TUG test is only designed to measure response in patients who are ambulatory. Given that LEMS is a rare condition and that no other effective treatments are available, public drug plans should consider reimbursement for patients who are not ambulatory, and therefore unable to complete the 3TUG test, on a case-by-case basis. This guidance is based on the opinion of clinical experts; no evidence evaluating a response to LEMS in patients who are not ambulatory was available for this review.</p> <p>For patients who are not ambulatory, alternative measurements may include various combinations of neurologic exams (e.g., cranial nerve testing, strength, reflexes), electrophysiology study (e.g., CMAP amplitude before and after max voluntary contraction performed before and after treatment), and the QMG score, depending on clinic resources.</p>
<b>Prescribing</b>		
3. The patient should be under the care of a neurologist with expertise in managing LEMS.	<p>There is potential for misdiagnosis or delayed diagnosis due to the rarity of LEMS.</p> <p>Accurate diagnosis by a clinician with experience and expertise in diagnosing and treating LEMS is important to ensure that amifampridine is prescribed for appropriate patients.</p>	<p>Patient access to a neurologist with experience in the management of LEMS may vary across jurisdictions, especially for those who live in rural areas. For such patients, a virtual assessment by a neurologist would be acceptable before prescribing amifampridine.</p>
<b>Pricing</b>		
4. A reduction in price.	<p>CADTH could not estimate the comparative efficacy of amifampridine phosphate versus best supportive care due to a lack of evidence. As such, the cost-effectiveness of amifampridine phosphate is unknown.</p> <p>Assuming comparable efficacy and safety with amifampridine base, a price reduction of at least 70% is required for amifampridine phosphate to be considered cost-effective at a willingness-to-pay threshold of \$50,000 per QALY. This estimate is subject to a high degree of uncertainty, and an additional price reduction may be warranted.</p>	—

Reimbursement condition	Reason	Implementation guidance
<b>Feasibility of adoption</b>		
5. The feasibility of adoption of amifampridine phosphate must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.	—

3TUG = Triple Timed-Up-and-Go; CMAP = compound muscle action potential; LEMS = Lambert-Eaton myasthenic syndrome; QALY = quality-adjusted life-year; QMG = quantitative myasthenia gravis.

## Discussion Points

- CDEC heard from clinical experts that amifampridine base is available through the Health Canada Special Access Programme and is the current standard of care for the treatment of all patients with LEMS. No other effective alternative treatment options are currently available.
- CDEC discussed the lack of a minimal important difference for the QMG or Subject Global Impression (SGI) scales in LEMS. CDEC and the expert consulted by CADTH noted that QMG is not the ideal scale to measure LEMS outcomes, given that it captures myasthenia gravis-specific elements (such as ocular and bulbar involvement) that are not expected to be affected by LEMS. Nevertheless, CDEC agreed with the expert that using a less specific scoring system, such as QMG, would bias against detection of a clinical benefit resulting from a pharmacological treatment.
- CDEC noted that patients without treatment experience and patients with paraneoplastic syndrome were not well represented in the study samples. According to the clinical expert, the treatment effect of amifampridine phosphate is not expected to differ substantially in these patient populations, although patients who are treatment naive may experience more side effects that may decrease over time.
- CDEC considered that best supportive care would be the appropriate comparator rather than amifampridine base in the pharmacoeconomic analysis if the base form is not marketed in Canada and not covered under public drug plans. CDEC suggests flexibility in the implementation of reimbursement recommendations related to various forms of amifampridine, to ensure patients are not penalized.

## Background

LEMS is a rare autoimmune disorder of the neuromuscular junction. In approximately 90% of patients with a LEMS diagnosis, it occurs as a result of the production of antibodies against the P- and Q-type voltage-gated calcium channels; this ultimately prevents muscle contraction. There are 2 forms of LEMS: paraneoplastic and primary autoimmune. Approximately 50% to 60% of LEMS cases are paraneoplastic and are most commonly associated with small-cell lung cancer. LEMS associated with other autoimmune diseases is referred to as primary autoimmune LEMS. Symptoms associated with both forms of LEMS include proximal muscle weakness, autonomic disturbance, and depressed tendon reflexes.

The estimated incidence of LEMS ranges from 0.2 to 0.5 per million and the prevalence of LEMS ranges from 2.3 to 2.6 per million based on published studies from Denmark, the Netherlands, and the US. Amifampridine, both the phosphate and base form, have been used as a first-line of therapy for both the paraneoplastic and primary autoimmune forms of LEMS in Canada and internationally for more than 30 years for the symptomatic treatment of LEMS, despite it not being commercially available in Canada until 2020.

Amifampridine phosphate is indicated for the symptomatic treatment of LEMS in adults. Amifampridine phosphate was granted priority review by Health Canada and received a Notice of Compliance (NOC) on July 31, 2020. Amifampridine phosphate is a broad-spectrum potassium channel blocker available in tablet form and the maximum total daily dosage recommended in the product monograph is 80 mg.

## Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of the 2 phase III, double-blind, randomized, discontinuation clinical studies and 1 bioequivalence study in adult patients with LEMS
- 1 patient testimonial
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with LEMS
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

### Patient Input

In absence of patient group input, 1 testimonial of the experiences of a Canadian individual with LEMS was accepted for this CADTH review given the rarity of LEMS in Canada.

The patient testimonial highlighted symptoms of LEMS, including worsening arm, core, and leg strength; dry mouth; difficulty swallowing; muscle weakness; and becoming fall prone. The patient specified that their disease experience led to their inability to continue working.

The patient was initially treated with pyridostigmine and then amifampridine. Treatment with amifampridine was reported to increase the patient's mobility and independence (e.g., ability to rise from a seated position without assistance, ability to navigate stairs safely) and symptoms (e.g., improvement in dry mouth and swallowing).

The patient testimonial highlighted the desire for improvement in muscle strength and bodily functions with the goal of performing daily activities with a sense of normalcy.

## Clinician Input

The clinical expert consulted by CADTH for this review identified access to amifampridine as the main unmet need for patients with LEMS as amifampridine has historically been accessed through compassionate use.

The clinical expert considers amifampridine to be the first line of therapy for the treatment of LEMS and agreed that there is no acceptable alternative to it for the symptomatic treatment of LEMS. Despite poorer prognosis for patients with the paraneoplastic form of LEMS, the clinical expert states that all patients with LEMS should have access to amifampridine.

Improvement in HRQoL and functional activities of daily living is the ultimate goal of treatment for patients with LEMS based on input from the clinical expert consulted by CADTH. The ideal assessment of treatment effect consists of the patient's subjective response, neurologic exam, Triple Timed-Up-and-Go (3TUG) test score (or alternative assessment), and electrophysiological study. However, variability in clinicians' assessment of response to treatment is noted in the Canadian clinical setting.

Diagnosis and treatment for patients with LEMS is overseen by a specialist in neurology. Assessment of response to treatment with amifampridine typically involves assessment at baseline (pre-treatment), once within the first month (typically within a week or 2 of initiation), and every 3 months until it is perceived by the treating clinician that the patient's symptoms are being appropriately managed.

The clinical expert states that patients who respond to amifampridine are expected to continue treatment for the duration of their life. Patients who discontinue treatment with amifampridine include patients whose symptoms do not improve based on a combination of the following: patient's subjective response, objective neurologic exam, 3TUG (or alternative assessment) score, and electrophysiological study.

## Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

**Table 2: Summary of Drug Plan Input and Clinical Expert Response**

Questions	CADTH response
<b>Considerations for initiation of therapy</b>	
Could the recommendation include implementation guidance or discussion points addressing the age restriction to provide some flexibility to consider pediatric patients?	The clinical expert suggested that pediatric patients are generally treated similarly to adult patients and maintained that amifampridine base and phosphate forms have a similar profile. However, the Health Canada-approved indication for amifampridine phosphate is limited to adult patients 18 years and older. Thus, CDEC is unable to make a recommendation beyond the target population set for this review.
<b>Considerations for continuation or renewal of therapy</b>	
Should the 3TUG test be limited to patients with LEMS who are ambulatory?	CDEC indicated that 3TUG score was not assessed in the LMS-002 trial and was exploratory in the LMS-003 trial. The T25WT was

Questions	CADTH response
	also suggested by the clinical expert as the closest alternate to the 3TUG test and either could be considered for patients who are ambulatory patients. However, the T25WT assessment was not found to be different in the LMS-002 study.
<b>Considerations for discontinuation of therapy</b>	
<p>Will loss of response be defined by anything other than the 3TUG test?</p> <p>If not, can a response to treatment be defined as an improvement of at least 30% on the 3TUG test? Also, can the 3TUG test be recommended only in patients who are ambulatory on a case-by-case basis.</p>	<p>CDEC agreed that the 3TUG test is only designed to measure response in patients who are ambulatory. Given that LEMS is a rare condition and that no other effective treatments are available, public drug plans should consider reimbursement for patients who are not ambulatory, and therefore unable to complete the 3TUG test, on a case-by-case basis. This guidance is based on the opinion of clinical experts; no evidence evaluating a response to LEMS in patients who are not ambulatory was available for this review.</p> <p>Alternative assessments may include various combinations of neurologic exams (e.g., cranial nerve testing, strength, reflexes), electrophysiology study (e.g., CMAP amplitude before and after max voluntary contraction performed before and after treatment), and QMG score, depending on clinic resources.</p>
<b>Considerations for prescribing of therapy</b>	
<p>Should patients be under the care of a neurologist with expertise in managing LEMS? Please include implementation guidance related to whether virtual assessment by a neurologist would be acceptable.</p>	<p>CDEC agrees that the patient should be under the care of a neurologist with expertise in managing LEMS, and virtual assessment by a neurologist would be acceptable.</p>
<b>System and economic issues</b>	
<ul style="list-style-type: none"> <li>• At a drug cost of \$21.90 per tablet, the annual treatment cost (including markup charges and dispensing fees) per patient for Firdapse was \$14,000 less costly relative to Ruzurgi. These cost savings are driven by the 20% lower unit price of Firdapse on a per-tablet basis compared to Ruzurgi (\$27.40 per 10 mg tablet).</li> <li>• The annual treatment cost of Firdapse is \$55,200 vs. \$69,000 for Ruzurgi.</li> <li>• The potential NOC withdrawal of Ruzurgi could impact pCPA negotiations for Firdapse.</li> <li>• Ruzurgi is under active negotiation at this time.</li> </ul>	<p>CDEC acknowledges the cost of amifampridine products and the issues with the NOC withdrawal.</p>

3TUG = Triple Timed-Up-and-Go; CDEC = Canadian Drug Expert Committee; CMAP = compound muscle action potential; LEMS = Lambert-Eaton myasthenic syndrome; NOC = Notice of Compliance; pCPA = pan Canadian Pharmaceutical Alliance; QMG = quantitative myasthenia gravis; T25WT = Timed 25 Foot Walk Test; vs. = versus.

## Clinical Evidence

### Description of Studies

Two pivotal trials, LMS-002 (N = 38) and LMS-003 (N = 26), were included in the CADTH systematic review. Both studies were phase III, multicenter, randomized, double-blind,

placebo-controlled withdrawal studies that aimed to assess the safety and efficacy of amifampridine phosphate for the treatment of LEMS in adult patients.

The LMS-002 study was composed of 4 parts in addition to an initial screening phase. The open-label run-in phase, in which all patients received amifampridine phosphate, allowed the investigator to titrate to the optimal dose regimen for each patient. Patients who were amifampridine phosphate naive were required to achieve a 3-point or higher improvement in QMG score from the score reported at screening. All patients were required to have received amifampridine (phosphate or base) for a minimum of 91 days and a stable dose of amifampridine phosphate for a minimum of 7 days. On day 1 of part 2, patients were randomized to either continue receiving the established amifampridine phosphate dose, or to taper treatment to placebo. Patients in the discontinuation group were tapered over the course of 7 days. On day 1 of part 3, patients in the discontinuation group received only placebo and continued with this regimen for 7 days. After the 14-day double-blind period of parts 2 and 3, all patients were transitioned to open-label amifampridine phosphate in the long-term safety phase of the trial.

The LMS-003 trial consisted of a 4-day double-blind withdrawal period. All patients were previously enrolled in an expanded access program and required to be on a stable dose of amifampridine phosphate for 1 week before randomization. Patients were randomized to either maintain their regular amifampridine phosphate dose or placebo for days 1 through 4. Efficacy assessments were conducted on day 0 and day 4 following the final blinded dose. Following the study, patients were permitted to return to the expanded access program.

## Efficacy Results

In the LMS-002 trial, patients who discontinued amifampridine phosphate treatment reported a statistically significant disease progression according to the coprimary end point of difference in QMG LS means of  $-1.7$  (95% CI,  $-3.4$  to  $-0.0$ ;  $P = 0.0452$ ). Though this result is statistically significant, it is below the identified clinically significant threshold of 2.6 units (note that this threshold was determined in patients with myasthenia gravis, no such threshold has been identified in patients with LEMS). Similarly, the coprimary end point of the LMS-003 trial was a difference in QMG LS means (95% CI), and it reported both a statistically and clinically significant difference with QMG LS means of  $-6.54$  (95% CI,  $-9.78$  to  $-3.29$ ;  $P = 0.0004$ ).

The second coprimary end point in both the LMS-002 and LMS-003 trials was SGI score. There was a statistically significant disease progression in patients who discontinued amifampridine phosphate according to difference in LS means (95% CI) in the LMS-002 study (QMG LS means = 1.8; 95% CI, 0.7 to 3.0;  $P = 0.0028$ ) and in the LMS-003 study (QMG LS means = 2.95; 95% CI, 1.53 to 4.38;  $P = 0.0003$ ). There was no clinically significant threshold identified for the SGI measure in patients with LEMS; however, the clinical expert consulted for this review considered the results to be clinically meaningful.

The LMS-002 trial included Clinical Global Impression – Improvement (CGI-I) as the first secondary end point, only to be formally tested if both coprimary end points were statistically significant. There was a statistically significant difference in LS means of  $-1.1$  (95% CI,  $-2.1$  to  $-0.1$ ;  $P = 0.0267$ ), favouring amifampridine phosphate. Given the statistical significance of CGI-I, the second secondary end point in the LMS-002 trial, Timed 25-Foot Walk Test, was formally tested. Patients discontinuing amifampridine phosphate showed a slight numerical

difference toward disease progression; however, no statistical significance was shown (LS means = 8.51; 95% CI, -26.77 to 43.79; P = 0.6274).

The LMS-003 trial included only 1 secondary end point, though there was no evidence that methods for controlling multiplicity were applied; therefore, definitive conclusions cannot be drawn. The LMS-003 study reported only postbaseline values as baseline CGI-I was not recorded, further negatively impacting the ability to interpret any apparent treatment differences. Patients in the amifampridine phosphate arm reported a postbaseline mean of 3.8 and patients in the placebo arm reported a postbaseline mean of 5.5; the nominal P value based on the Wilcoxon Rank Sum Test was 0.0020.

## Harms Results

In the LMS-002 trial, adverse events (AEs) were reported separately through the different phases of the trial. During the open-label run-in phase, AEs were reported for 53 patients, including those who would eventually withdraw from the trial. AEs were reported in ■ of patients who were treatment naive and ■ of patients with treatment experience. The most commonly reported AEs were paresthesia (34.0%) and oral paresthesia (39.6%).

In total, 25% of patients experienced serious AEs during the open-label safety extension, 1 of which was fatal small-cell lung cancer. All but 2 were deemed by the investigator to be unrelated to the study drug, while the serious AEs deemed probable to be related to the study drug were managed by dose reduction. In the LMS-003 study, AEs were reported in 23.1% of patients receiving amifampridine phosphate and ■ of patients in the placebo group. The most common AEs reported were muscular weakness (38.5%) and fatigue (30.8%), though these were both in the placebo group and common symptoms of LEMS progression itself; therefore, there is uncertainty surrounding whether safety signals are due to treatment side effects or disease progression itself.

## Critical Appraisal

Both of the LMS-002 and LMS-003 trials were double-blind studies that employed various strategies to maintain blinding of the patients, investigator, site personnel, and sponsor personnel. However, by designing a study using a withdrawal enrichment strategy, partial unblinding was possible as patients in the placebo arm were anticipated to experience deterioration before amifampridine phosphate being reinstated. Unblinding in the LMS-002 and LMS-003 studies may have biased subjective patient-assessed (e.g., SGI) and investigator-assessed (e.g., QMG, CGI-I) outcome results in favour of amifampridine phosphate.

The coprimary end points for the LMS-002 and LMS-003 trials were QMG and SGI scores. QMG is a measure developed for use in myasthenia gravis and includes components relating to ocular and bulbar involvement that are more relevant to myasthenia gravis and not expected to be impacted by treatment for LEMS. While the QMG was not considered a relevant assessment tool in LEMS by the clinical expert consulted by CADTH, as it was designed and validated for the assessment of myasthenia gravis, the components of QMG that are unrelated to LEMS would bias the results against amifampridine phosphate. The change in the QMG components that are expected to be impacted by treatment would need to be more pronounced to reach statistical significance.

Subgroup analysis based on type of LEMS (paraneoplastic versus primary autoimmune) were not performed in the LMS-002 or LMS-003 trials. The LMS-003 study did present results stratified by high dose ( $\geq 60$  mg per day) and low dose ( $< 60$  mg per day), which can be considered a rough proxy for disease severity according to the clinical expert, though the study was not powered to detect differences in this subgroup. Whether or not the treatment effect differs between subgroups identified as relevant in the CADTH review protocol (i.e., primary autoimmune versus paraneoplastic) remains unknown.

The withdrawal enrichment strategy used in the LMS-002 and LMS-003 trials resulted in a highly selected study population of patients who were treatment experienced and responsive to amifampridine phosphate at baseline. Aspects of the trial design resulted in a study population that exhibited a magnitude of treatment response that may not be generalizable to patients in Canada who are treatment naive, including those who are newly diagnosed with LEMS. It should be noted that the withdrawal design lends itself to the LEMS population that includes heterogeneity among “fast” and “slow” amifampridine metabolizers, requiring the inclusion of a dose titration phase for patients who are treatment naive.

Overall, the baseline characteristics of patients in the LMS-002 and LMS-003 trials were generally consistent with the Canadian clinical population currently treated with amifampridine phosphate. However, in the LMS-002 and LMS-003 studies, 15.8% and 23.1% of patients had paraneoplastic syndrome, respectively, likely due to the requirement for patients to have completed anti-cancer treatment at least 3 months before screening. This is inconsistent with the clinical population, where it is estimated that 50% to 60% of patients have paraneoplastic syndrome. Patients with paraneoplastic LEMS are known to have poorer prognosis due to the underlying neoplastic condition; thus, the results of the LMS-002 and LMS-003 studies may not be representative of these patients. It is noted that the clinical expert consulted did not expect there to be major differences in treatment efficacy of amifampridine phosphate based on these subgroups of patients.

There was notable inconsistency in the 2 trials, specifically in the magnitude of change in QMG score. In the LMS-002 study, conducted in 2011, the change was 1.7, which was below the recognized minimally important difference, though this threshold has not been validated in patients with LEMS. There was also an imbalance in QMG score at the baseline assessment (6.4 versus 5.6; difference of 0.8), possibly due to random sampling error amplified by the small sample size. When considering the small difference in QMG score between treatment groups, numerically, half the change at day 14 could potentially be explained by the unbalanced baseline value. In the LMS-003 trial, which was conducted more recently in 2017, the change in QMG score was much higher, at 6.5, though with a similar imbalance in baseline values. The inconsistency between trials was less pronounced in the SGI end point, though a smaller change was reported in the LMS-002 trial than in the LMS-003 trial (1.8 versus 3.0). These differences cast some uncertainty on the treatment effect. However, given that the LMS-003 study was conducted exclusively in the US, where practice may be less variable and closer to the Canadian context, and given possible change over the past decades in patient treatment modality, this trial can be considered more generalizable to the current setting and more reliable in design.

## Other Relevant Evidence

The sponsor evaluated the relative bioavailability of amifampridine phosphate in a randomized, crossover trial (the DAPSEL study). In this trial, the sponsor compared the formulations of amifampridine phosphate salt (in tablet formulation) with amifampridine

base (in capsule formulation) to determine their relative bioequivalence. Statistical evaluation was performed for the area under the curve up to the last measurable concentration ( $AUC_{0-t}$ ) and maximum plasma concentration ( $C_{max}$ ) with ANOVA and the 90% CI for the ratio of reference formulation (amifampridine phosphate salt) over the test formulation (amifampridine base) were calculated. The area under the curve ratio had fallen within the prespecified bioequivalence limits (80% to 125%). For the  $C_{max}$ , the observed inferior limit exceeded the 80.0% bound and was near the 75% bound proposed for highly variable drugs, leading regulators to note that the efficacy profiles of the formulations would not be expected to differ.

## Economic Evidence

**Table 3: Cost and Cost-Effectiveness**

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target population	Adult patients with LEMS
Treatment	Amifampridine phosphate (Firdapse)
Submitted price	Amifampridine phosphate: \$21.90 per 10 mg tablet
Treatment cost	The annual cost of amifampridine phosphate is \$51,993 per patient
Comparator	Amifampridine base (Ruzurgi)
Perspective	Canadian publicly funded health care payer
Time horizon	One year
Key data sources	Sponsor undertook a narrative comparison of amifampridine phosphate (studies LMS-002 and LMS-003) and amifampridine base (DAPPER) and 1 bioequivalence study (DAPSEL)
Costs considered	Drug acquisition costs, dispensing fees, and markups
Key limitations	<ul style="list-style-type: none"> <li>The comparative clinical efficacy of amifampridine phosphate and amifampridine base is uncertain, as the unadjusted naive comparison was not assessed in the clinical review due to the lack of supporting evidence. Naive comparisons are associated with significant methodological limitations. However, CADTH notes that the bioequivalence data suggest similarity between amifampridine phosphate and amifampridine base with regards to <math>AUC_{0-t}</math> and <math>C_{max}</math>.</li> <li>The sponsor’s analysis included markups and dispensing fees that were inappropriately estimated; thus, overestimated the cost savings associated with amifampridine phosphate compared to amifampridine. The CADTH reanalysis excluded markup and dispensing fees.</li> <li>Amifampridine base was recently withdrawn from the market. As such, the most appropriate comparator is BSC. No information on the relative effectiveness or cost-effectiveness of amifampridine phosphate with BSC was submitted to CADTH. In the absence of comparative evidence, the cost-effectiveness of amifampridine phosphate is highly uncertain. If an agreement is reached on amifampridine base, the presence of a confidential price would impact any comparative cost findings.</li> </ul>

Component	Description
<b>CADTH reanalysis results</b>	<p>In CADTH reanalysis, when removing markup and dispensing fees, treatment with amifampridine phosphate resulted in estimated annual cost savings of \$13,058 per patient compared with amifampridine base.</p> <p>No assessment of the cost-effectiveness of amifampridine phosphate with BSC could be undertaken. Amifampridine phosphate costs between \$11,990 and \$63,948 per patient each year.</p>

AUC<sub>0-t</sub> = area under the curve up to the last measurable concentration, BSC = best supportive care; C<sub>max</sub> = maximum plasma concentration; LEMS = Lambert-Eaton myasthenic syndrome.

## Budget Impact

CADTH identified the following limitations with the sponsor's submission: uncertainty in currently funded treatments for LEMS, uncertainty in the market uptake of amifampridine phosphate, and uncertainty in the availability and relative dosing of amifampridine base.

CADTH revised the sponsor's base case by removing all market share for amifampridine base. Although the sponsor's budget impact analysis suggested budgetary savings, based on CADTH reanalysis, the 3-year budget impact associated with the reimbursement of amifampridine phosphate is expected to be \$7,829,989 (\$2,417,345 in year 1; \$2,450,841 in year 2; and \$2,961,803 in year 3).

## CDEC Information

### Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunskey, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

**Meeting date:** April 27, 2022

**Regrets:** Two expert committee members did not attend.

**Conflicts of interest:** None