CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Amifampridine phosphate (Firdapse)

Indication: For the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults

Sponsor: KYE Pharmaceuticals Inc.

Recommendation: Reimburse with Conditions

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AMIFAMPRIDINE PHOSPHATE (FIRDAPSE— KYE PHARMACEUTICALS)

Therapeutic Area: Lambert-Eaton myasthenic syndrome (LEMS)

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 II 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 LMS-002, patients who discontinued amifampridine phosphate treatment reported a statistically significant disease progression according to the co-primary endpoint of difference in Quantitative Myasthenic Gravis (QMG) Least Squares (LS) means (95% Confidence Interval [CI]) of -1.7 (-3.4, -0.0), p = 0.0452, compared with patients who continued to receive the drug. Similarly, patients in LMS-003 who discontinued amifampridine phosphate reported both a statistically and clinically significant QMG LS means difference of -6.54 (-9.78, -3.29), p = 0.0004.

Patients and the clinical expert identified a need for treatments that can improve activities of daily living and HRQoL. The effect of amifampridine on health-related quality of life (HRQoL) and productivity was not evaluated in the LMS-002 and LMS-003 studies and 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 in order to achieve a willingness to pay threshold of $50,000 per QALY.

Table 1: Reimbursement Conditions and Reasons

Reimbursement Condition	Reason	Implementation Guidance
Initiation		
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 Heath Canada indication specifies that amifampridine is only to be used in patients 18 years of age and older.	—
Renewal		
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 as their primary outcome, clinical experts noted that the 3TUG is the preferred outcome measure used in clinical practice and that titration to the optimal effective dose requires between 2 and 3 months.	The 3TUG test is only designed to measure response in ambulatory patients. 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 non-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 non-ambulatory patients was available for this review. 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.
Prescribing		
3. The patient should be under the care of a neurologist with expertise in managing LEMS	There is potential for misdiagnosis or delayed diagnosis due to the rarity of LEMS. 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.	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.
Pricing		
4. A reduction in price	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. Assuming comparable efficacy and safety with amifampridine base, a price reduction of at least 70% is required for	—

Reimbursement Condition	Reason	Implementation Guidance
	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 additional price reduction may be warranted.	
Feasibility of Adoption		
1. 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; QMG = quantitative myasthenia gravis

Discussion Points

- CDEC heard from clinical experts that amifampridine base is available through the Health Canada Special Access Programme (SAP) 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 (MID) for the QMG or SGI in LEMS. CDEC and the expert noted that QMG is not the ideal scale to measure LEMS outcomes, since 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 would bias against detection of a clinical benefit resulting from a pharmacological treatment.
- CDEC noted that treatment-naive patients and patients with paraneoplastic syndrome were not well represented in the study samples. According to the clinical expert, treatment effect of amifampridine phosphate is not expected to differ substantially in these patient populations, although treatment-naive patients 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 pharmaceoeconomic 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

Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder of the neuromuscular junction. In approximately 90% of diagnosed patients, LEMS occurs as a result of the production of antibodies against the P/Q type voltage-gated calcium channels; this ultimately prevents muscle contraction. There are two 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 (SCLC). 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 paraneoplastic and primary autoimmune forms of LEMS in Canada and internationally for over 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 their 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
- Patients perspectives was provided by 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, one 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 of patients with the paraneoplastic form of LEMS, the clinical expert states that all patients with LEMS should have access to amifampridine.

Improvement in health-related quality of life (HRQoL) and functional ADLs 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, neurological exam, Triple Timed Up and Go (3TUG) test (or alternative assessment), and electrophysiological study. However, variability in clinicians' assessment of response to treatment is noted in the Canadian clinical setting.

The 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 two of initiation), and every three 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 throughout 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 neurological exam, 3TUG (or alternative assessment), 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
Considerations for initiation of therapy	
Ruzurgi has HC indication for 6 years of age and older; Firdapse only for adult patients 18 years of age and older. Discussion point for Ruzurgi recommendation notes that although patients enrolled in the DAPPER study ranged from 23 to 83 years of age, given the general mechanism of action, amifampridine is expected to be effective across age groups covered by the Health Canada indication. Pediatric patients are generally treated similarly to adult patients according to clinical expert. • 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 of age and older. Thus, CDEC is unable to make a recommendation beyond the target population set for this review.
Considerations for continuation or renewal of therapy	
Consider alignment with Ruzurgi renewal criteria. The 3TUG test is appropriate for ambulatory patients with LEMS.	CDEC indicated that 3TUG was not assessed in LMS-002 and was exploratory in LMS-003. T25MWT was also suggested by the clinical expert as the closest alternate to the 3TUG and this too could be considered. This assessment was not found to be different on LMS-002. Considering the variability of resources across Canada, a combination of assessments as determined by the treating physician would be reasonable.
Considerations for discontinuation of therapy	
Will loss of response be defined by anything other than the 3TUG test? If not, consider alignment with Ruzurgi - A response to treatment is defined as an improvement of at least 30% on the 3TUG test. Also, consider alignment with Ruzurgi for implementation guidance re: 3TUG test only in ambulatory patients. Case-by-case assessment for non-ambulatory patients.	CDEC agreed that the 3TUG test is only designed to measure response in ambulatory patients. 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 non-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 non-ambulatory patients was available for this review. 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 the QMG score, depending on clinic resources.
Considerations for prescribing of therapy	
Consider alignment with Ruzurgi – The patient should be under the care of a neurologist with expertise in managing LEMS. Include the same implementation guidance re: virtual assessment by a neurologist would be acceptable	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.

Questions	CADTH Response
System and economic issues	
• Drug cost $21.90 per tablet. The annual treatment costs (including mark-up charges and dispensing fees) per patient for FIRDAPSE was $14K less costly relative to that of Ruzurgi. These cost-savings are driven by the 20% lower unit price of FIRDAPSE on a per-tablet basis compared to Ruzurgi ($27.40/ 10 mg tablet). • Annual treatment cost $55,200 vs $69,000 for Ruzurgi. • The potential NOC withdrawal of Ruzurgi could impact pCPA negotiations for Firdapse. • Ruzurgi is under active negotiation at this time.	CDEC acknowledges the cost of amifampridine products and the issues with the NOC withdrawal.

3TUG = triple timed up and go; CDEC = Canadian Drug Expert Committee; HC = Health Canada; LEMS = Lambert-Eaton Myasthenic Syndrome; NOC = notice of compliance; pCPA = pan Canadian Pharmaceutical Alliance; QMG = quantitative myasthenia gravis

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.

LMS-002 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 that were amifampridine phosphate naïve were required to achieve a ≥3-point improvement in Quantitative Myasthenic Gravis (QMG) 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.

LMS-003 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 prior to 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 LMS-002, patients who discontinued amifampridine phosphate treatment reported a statistically significant disease progression according to the co-primary endpoint of difference in QMG Least Squares (LS) means (95% Confidence Interval [CI]) of -1.7 (-3.4, -0.0), with a P value of 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 Myasthenia Gravis [MG] patients, no such threshold has been identified in patients with LEMS). Similarly, the co-primary endpoint of LMS-003 was difference in QMG LS means (95% CI), reporting both a statistically and clinically significant difference of -6.54 (-9.78, -3.29), with a P value of 0.0004.

The second co-primary endpoint in both LMS-002 and LMS-003 was Subject Global Impression (SGI). There was a statistically significant disease progression in patients that discontinued amifampridine phosphate according to difference in LS means (95% CI)

in LMS-002, 1.8 (0.7, 3.0), P value of 0.0028, and in LMS-003, 2.95 (1.53, 4.38), P value of 0.0003. There was no clinically significant threshold identified for the SGI measure in LEMS patients, however the clinical expert consulted for this review considered the results to be clinically meaningful.

LMS-002 included Clinical Global Impression – Improvement (CGI-I) as the first secondary endpoint, only to be formally tested if both co-primary endpoints were statistically significant. There was a statistically significant difference in LS means (95% CI) of -1.1 (-2.1, -0.1), P value of 0.0267, favouring amifampridine phosphate. Given the statistical significance of CGI-I, the second secondary endpoint in LMS-002, timed 25-foot walk (T25FW), was formally tested. Patients discontinuing amifampridine phosphate showed a slight numerical difference towards disease progression, however the difference in LS means (95% CI) showed no statistical difference, 8.51 (-26.77, 43.79), P value of 0.6274.

LMS-003 included only one secondary endpoint, though there was no evidence that methods for controlling multiplicity were applied and therefore definitive conclusions cannot be drawn. LMS-003 reported only post-baseline 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 post-baseline mean of 3.8 and patients in the placebo arm reported a post-baseline mean of 5.5, nominal P value based on the Wilcoxon Rank Sum Test was 0.0020.

Harms Results

In LMS-002, 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 that would eventually withdraw from the trial. AEs were reported in [redacted] of treatment-naïve patients and [redacted] in treatment experienced patients. The most commonly reported AEs were paresthesia (34.0%) and oral paresthesia (39.6%).

25% of patients experienced serious adverse events (SAEs) during the open-label safety extension, one of which was fatal SCLC. All but 2 were deemed by the investigator to be unrelated to the study drug, while the SAEs deemed probable to be related to the study drug were managed by dose reduction. In LMS-003, AEs were reported in 23.1% of patients receiving amifampridine phosphate and [redacted] 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 LMS-002 and LMS-003 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 prior to amifampridine phosphate being reinstated. Unblinding in LMS-002 and LMS-003 may have biased subjective patient-assessed (e.g., SGI) and investigator-assessed (e.g., QMG, CGI-I) outcome results in favor of amifampridine phosphate.

The co-primary endpoints for both LMS-002 and LMS-003 were QMG and SGI. 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 MG, 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 LMS-002 or LMS-003. LMS-003 did present results stratified by high dose (≥60 mg/day) and low dose (<60 mg/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 (e.g., primary autoimmune vs. paraneoplastic) identified as relevant in the CADTH review protocol remains unknown.

The withdrawal enrichment strategy used in both LMS-002 and LMS-003 resulted in a highly selected study population of patients that 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 Canadian patients who are treatment-naive, including those who are newly diagnosed with LEMS. It should be noted, 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 treatment-naïve patients.

Overall, the baseline characteristics of patients in LMS-002 and LMS-003 were generally consistent with the Canadian clinical population currently treated with amifampridine phosphate. However, in LMS-002 and LMS-003, 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 prior to 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 LMS-002 and LMS-003 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 the QMG. In LMS-002, conducted in 2011, the change was 1.7, which was below the recognized minimally important difference (MID), 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 vs. 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 between treatment groups, numerically, half the change at Day 14 could potentially be explained by the unbalanced baseline value. The change in QMG was much higher at 6.5, though with a similar imbalance in baseline values, in LMS-003, which was conducted more recently in 2017. The inconsistency between trials was less pronounced in the SGI endpoint, though a smaller change was reported in LMS-002 than in LMS-003 (1.8 vs. 3.0). These differences cast some uncertainty on the treatment effect. However, since LMS-003 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 sponsors 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 AUC(0-t) and Cmax with ANOVA and the 90% CI for the ratio of reference formulation (amifampridine phosphate salt) over the test formulation (amifampridine base) were calculated. The AUCs ratio had fallen within the pre-specified bioequivalence limits (80-125%). For the maximum plasma concentration (Cmax), the observed inferior limit exceeded the 80.0% bound and was near the 75% bound proposed for highly variable drugs, leading to regulators noting 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

Component	Description
Key data sources	Sponsor undertook a narrative comparison of amifampridine phosphate (LMS-002 and LMS-003) and amifampridine base (DAPPER) and one bioequivalence study (DAPSEL)
Costs considered	Drug acquisition costs, dispensing fees and mark-ups
Key limitations	• The comparative clinical efficacy of amifampridine phosphate and amifampridine base is uncertain, as the unadjusted naïve comparison was not assessed in the clinical review due to the lack of supporting evidence. Naïve 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 $AUC_{0-\infty}$ and C_{max}. • The sponsor's analysis included markups and dispensing fees which were inappropriately estimated and thus, over-estimated the cost-savings associated with amifampridine phosphate compared to amifampridine. CADTH reanalysis excluded markup and dispensing fees. • 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. As such, 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.
CADTH reanalysis results	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. 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.

BSC = best supportive care; 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 market uptake of amifampridine phosphate and uncertainty in 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 BIA suggested budgetary savings, based on CADTH reanalysis, the three-year budget impact associated with the reimbursement of amifampridine phosphate is expected to be $7,829,989 (year 1: $2,417,345, year 2: $2,450,841, and year 3: $2,961,803 in year 3).

Canadian Drug Expert Committee (CDEC) Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, 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

2 expert committee member(s) did not attend.

Conflicts of Interest

None