CADTH

CADTH Drug Reimbursement Review

Pharmacoeconomic Report

AMIFAMPRIDINE (RUZURGI)

(Médunik Canada Inc.)

Indication: For the symptomatic treatment of Lambert-Eaton myasthenic syndrome in patients 6 years of age and older.

Service Line: CADTH Common Drug Review
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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

3TUG	Triple-Timed Up-and-Go
BIA	budget impact analysis
BSC	best supportive care
ICER	incremental cost-effectiveness ratio
IVIg	intravenous immunoglobulin
LEMS	Lambert-Eaton myasthenic syndrome
MG	myasthenia gravis
QALY	quality-adjusted life-year
QMG	quantitative myasthenia gravis
WTP	willingness to pay

Executive Summary

The executive summary is composed of 2 tables (Table 1: Submitted for Review and Table 2: Summary of Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Amifampridine (Ruzurgi) 10 mg tablet
Submitted price	Amifampridine 10 mg tablet: $27.40
Indication	For the symptomatic treatment of LEMS in patients 6 years of age and older
Health Canada approval status	NOC
Health Canada review pathway	Priority review
NOC date	August 10, 2020
Reimbursement request	As per indication
Sponsor	Médunik Canada Inc.
Submission history	Previously reviewed: No

LEMS = Lambert-Eaton myasthenic syndrome; NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	LEMS in patients 6 years of age and older
Treatment	Amifampridine in combination with BSC
Comparator	BSC alone (assumed to consist of symptom management, possibly including pyridostigmine, immunosuppressants, IVIg, and/or PLEX)
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	Lifetime (54 years)
Key data source	Cochrane review Randomized controlled trials by Sanders (2000) and Oh (2009)
Submitted results for base case	ICER = $453,809 per QALY (incremental cost: $956,144; incremental QALY: 2.11)
Key limitations	• The sponsor estimates incremental effectiveness using QMG scores. CADTH's clinical review found that QMG score is not considered an appropriate or relevant assessment tool for LEMS. The QMG primarily captures symptoms within the upper body, whereas LEMS symptoms primarily affect a patient's mobility. Consequently, the sponsor's model does not reflect the true impact of treatment with amifampridine + BSC on quality-adjusted survival and cost-effectiveness. • The sponsor's model assumes that QMG scores would be stable for patients treated with amifampridine, but that QMG scores would worsen by 10% per year for patients treated with BSC alone. This assumption that LEMS worsens with BSC alone is not supported by clinical evidence, and results in all BSC patients being in the worst possible health state within 5 years. This finding raises serious concerns about the model's face validity. • The sponsor's model categorizes patients into severity-based categories, assigning health utilities based on the mean value for each category. This model structure produces inappropriate assumptions about the relationship between small changes in QMG at the threshold of each category, meaning that small QMG changes at borders between categories may have a disproportionate effect on QALYs.

Component	Description
	• Due to these limitations, the cost-effectiveness of amifampridine treatment could not be estimated from the sponsor's submitted evidence, nor could a price-reduction analysis be conducted.
CADTH reanalysis results	• No CADTH reanalysis was conducted, given the model's structural limitations and reliance on QMG scores to calculate QALYs. • An exploratory analysis of the sponsor's base case found that 92% of the sponsor's estimate of incremental QALY was produced by assuming that LEMS worsens on BSC alone. Without this assumption, the sponsor's reported incremental QALY benefit would have been 0.17, and the corresponding ICER would have been $6.4 million per QALY.

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; IVIg = intravenous immunoglobulin; LEMS = Lambert-Eaton myasthenic syndrome; PLEX = plasma exchange; QALY= quality-adjusted life-year; QMG = quantitative myasthenia gravis.

Conclusions

The CADTH review of the clinical evidence suggests that treatment with amifampridine may reduce disability related to the progression of Lambert-Eaton myasthenic syndrome (LEMS) during the observation period in clinical trials, but found that the effect of amifampridine on health-related quality of life was unknown, as was the generalizability of the patient population to a Canadian population. The clinical experts consulted by CADTH suggested that a Timed Up-and-Go test would be a more appropriate method of estimating the clinical effectiveness of treatment.

CADTH did not conduct a reanalysis of the sponsor's cost-effectiveness model due to the serious limitations in the model's structure and its reliance on the quantitative myasthenia gravis (QMG) score to derive incremental effectiveness. Exploratory analyses conducted by CADTH found that 92% of the sponsor's estimate of incremental quality-adjusted life-years (QALYs) arose from the sponsor's assumption that QMG scores worsen by 10% per year with best supportive care (BSC) alone, but not with amifampridine. This assumption is unsupported by evidence from the literature and produces results that lack face validity. It also produces a strong bias in favour of amifampridine: an exploratory analysis suggested that the incremental cost-effectiveness ratio (ICER) is greater than $6 million per QALY with this assumption removed. While this result is numerically greater than the sponsor's base case ($453,809 per QALY for amifampridine + BSC versus BSC alone), the conclusions are similar, given that the sponsor's submitted base case found a 0% probability of amifampridine being cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY.

The inappropriate outcome measure used in the analysis coupled with the limitations of the model's structure and assumptions mean that the cost-effectiveness of amifampridine + BSC for the treatment of LEMS is unknown. The sponsor's estimate of the clinical effectiveness of amifampridine on QMG score does not meet the minimum QMG score threshold considered relevant to patients, suggesting that it is unlikely to provide value, given the high cost of treatment.

Stakeholder Input Relevant to the Economic Review

This section is typically a summary of the feedback received from the patient groups that participated in the CADTH review process. However, no patient group input was received for this review following CADTH's call for patient input. Given that LEMS is a rare disease in Canada, CADTH accepted a testimonial from a Canadian individual with LEMS who described their experience.

The patient reported being treated with pyridostigmine and intravenous immunoglobulin (IVIg) therapy, and said that it did not have any significant effect on their condition. The patient received amifampridine and reported improved effects in several symptom areas, including ability to rise from a seated position, dry mouth and swallowing symptoms, and ability to navigate stairs. The patient identified the cost of the drug as one of the main concerns; they believe that the drug would likely be unaffordable (and access to it would be restricted) if it is not reimbursed.

Economic Review

The current review is for amifampridine (Ruzurgi) for the symptomatic treatment of LEMS in patients 6 years of age and older.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis[1] of amifampridine + BSC versus BSC alone for the symptomatic treatment of LEMS in patients 6 years of age and older. Both major forms of LEMS were considered: primary autoimmune LEMS and paraneoplastic LEMS. The sponsor assumed that BSC comprises some combination of pyridostigmine, immunosuppressants, IVIg, and/or plasma exchange, with the degree to which each of these is utilized (and the resulting cost of BSC) depending upon disease severity (health state), type of LEMS (primary autoimmune or paraneoplastic), and whether BSC is provided alone or in combination with amifampridine.

This target population aligns with the Health Canada–indicated population and reimbursement request. The perspective was that of the Canadian publicly funded health care payer. A lifetime time horizon was adopted, which involved following a hypothetical cohort of 57-year-old patients for 54 years. The Markov model had a monthly cycle length. The discount rate was 1.5% per annum, in accordance with CADTH's guidelines.

Amifampridine is available as a single tablet, containing 10 mg amifampridine for oral administration, at a cost of $27.40 per tablet. The sponsor's assumed daily dosage of amifampridine was 40 mg to 100 mg (depending upon the severity of LEMS), corresponding to a cost of $3,336 to $8,339 per month or $40,027 to $100,067 per year. The maximum cost of BSC was assumed to be $1,329 per month, or $15,946 per year.

Resource utilization for both amifampridine and BSC was assumed to increase proportionately with disease severity, with the highest costs applied to patients with primary

autoimmune LEMS in the severe health state. It should be noted that pyridostigmine was not considered as a separate comparator in the economic evaluation, but rather as a component of BSC.

The main outcome measure was QMG score. The sponsor described the QMG assessment as "a standardized, quantitative assessment of the function of muscle groups typically involved in MG [myasthenia gravis] and LEMS." QMG scores range from 0 to 39, with higher scores indicating greater disease severity. The sponsor calculated a common baseline QMG score for all patients, then applied an improvement (reduction) in QMG score for patients treated with amifampridine + BSC but not for patients treated with BSC alone. The sponsor also assumed that QMG scores would worsen by 10% per year following treatment with BSC alone, but would not worsen over time following treatment with amifampridine + BSC. Discrete health states were defined based on specific ranges of QMG scores, and QALYs were calculated by assigning health utilities based on the midpoint QMG score for each health state.

Model Structure

The sponsor submitted a Markov model with a monthly cycle length, with transition probabilities informed by a microsimulation model. The 5 health states in the Markov model were based on categories of disease severity based on QMG score:

- "asymptomatic" (QMG score 0 to 1)
- "mild" (QMG score 2 to 7)
- "moderate" (QMG score 8 to 15)
- "severe" (QMG score 16 to 39)
- "dead."

Following treatment, patients entered the model through any of the first 4 health states. After each cycle, patients could move to the next more severe health state (worsening of symptoms), remain in the same health state, or move to the dead state. Patients could also reach disease remission. The sponsor's figure describing the model is provided in Appendix 3. Note that remission, while appearing to be a mutually exclusive state in the sponsor's figure in Appendix 3, is not modelled as such; rather, all patients in remission are simultaneously modelled as members of the mild health state.

Model Inputs

The sponsor cited a 2011 Cochrane review by Keogh (2011)[2] that estimated the impact of LEMS treatment on QMG score. This review included 4 randomized controlled trials investigating amifampridine, with a total of 54 patients: Sanders (2000),[3] McEvoy (1989),[4] Wirtz (2009),[5] and Oh (2009).[6] Of these, only Sanders (2000) and Oh (2009) were included in the Cochrane review's meta-analysis of QMG assessment results.

Sanders (2000) reported an average QMG score of 8.50 with amifampridine + BSC (n = 12) and of 12.30 with BSC alone (n = 14). Oh (2009) reported an average QMG score of 13.00 with amifampridine + BSC (n = 6) and of 13.00 with BSC alone (n = 6). The sponsor derived a simple weighted average of these 4 QMG scores by multiplying each by the respective sample size and dividing the sum of these by the total sample size (38). The resulting weighted average (11.32) was used as a common baseline QMG score for both amifampridine + BSC and BSC alone.

The sponsor assumed that the final QMG score following treatment with amifampridine + BSC would decrease (improve) by 2.44 points (95% confidence interval, 1.22 points to 3.65 points), as per the Cochrane review's meta-analysis of QMG results, and assumed that the final QMG score following treatment with BSC alone would remain at baseline.

The sponsor then conducted a microsimulation of 1,000 patients to distribute patients across initial health states, based on the assumptions described earlier. Because the baseline QMG score for both amifampridine + BSC and BSC alone was assumed to be 11.32 (standard deviation 4.34), and because QMG scores following treatment with BSC alone were assumed to remain at baseline (prior to worsening), the average final QMG score following treatment with BSC alone remained at 11.32. Across the 1,000 patients in the microsimulation, the lowest QMG score following treatment with BSC alone was 9.43, while the highest was 13.09. Given that the entire range of scores lay within the bracket for moderate LEMS (i.e., a QMG score of 8 to 15), the sponsor assumed that 100% of patients would remain in the moderate health state following treatment with BSC alone (prior to worsening). Meanwhile, the 1,000 simulated QMG scores following treatment with amifampridine + BSC lay in the range of 7.02 to 10.67, with 7.6% categorized as mild (QMG score 2 to 8) and 92.40% categorized as moderate (QMG score 8 to 16).

The sponsor assumed no worsening of QMG score over time following treatment with amifampridine + BSC. However, following treatment with BSC alone, a worsening rate of 10% per annum was assumed. As a result of this assumption, the QMG scores for all patients treated with BSC alone in the sponsor's microsimulation model (used to inform the transition probabilities used in the sponsor's Markov model) were assumed to increase by 10% per year, eventually reaching 39 (the maximum possible QMG score) for every patient. This means that all patients treated with BSC alone were assumed by the sponsor to eventually transition to the severe health state (unless they died first), whereas all patients treated with amifampridine + BSC were assumed to remain in the mild or moderate health state until death. Note that the sponsor's assumed 10% per annum worsening rate for BSC alone is in line with the assumption adopted in an economic evaluation of Firdapse conducted by the Polish firm MAHTA (2018),[7] although the authors of the MAHTA study acknowledged that this estimate was not evidence-based, given that there are no studies in patients with LEMS that allow estimation of the long-term trend of the severity of the disease.

The probability of remission was derived from the study by Lipka (2020),[8] which reported a 3.33% probability of full remission at a median follow-up of 4 years. The sponsor converted this into a monthly probability of remission of 0.07%. The sponsor assumed that all patients in remission would simultaneously be classified as being in the mild health state and continue treatment.

Survival with primary autoimmune LEMS was assumed to be similar to that of the general population, with age- and sex-matched mortality rates derived from Statistics Canada life tables, weighted by the demographic characteristics of patients in the Sanders (2000) and Oh (2009) studies. Survival with paraneoplastic LEMS was estimated using a prospective observational cohort study of 31 patients with paraneoplastic LEMS and 279 patients with small cell lung cancer only. The sponsor fitted 8 different parametric survival curves to extrapolate long-term survival; while the model allows the user to choose any one of these 8 parametric distributions, the sponsor's choice was the log-logistic distribution. This was justified by the sponsor on the basis that it minimized statistical measures of goodness of fit (Akaike's and Bayesian Information Criterion — AIC and BIC) and provided an "excellent

visual fit to the Kaplan-Meier curve throughout the trial follow-up." The log-logistic distribution also appeared to result in greater survival beyond 10 years than all other distributions considered ().

Only adverse events with reported incidence of greater than or equal to 5% on the product monograph in at least 1 treatment arm were considered: dysesthesia, abdominal pain, dyspepsia, nausea, back pain, muscle spasms, dizziness, and hypoesthesia.

Doses of amifampridine were assumed to differ by health state:

- 40 mg for patients who were 'asymptomatic'
- 60 mg for patients in the 'mild' health state
- 80 mg for patients in the 'moderate' health state
- 100 mg for patients in the 'severe' health state.

The health-state utility values associated with each severity category (health state) were derived from those used in the MAHTA study (2018).[7] According to the sponsor, "the authors used a questionnaire distributed to some physicians to estimate the utility associated with patients with asymptomatic LEMS (QMG: 0–1), as well as patients with a mild form (QMG: 2–7), moderate form (QMG: 8–15) and severe form (QMG: 16–39) of the disease. According to [key opinion leader] opinion, this set of utility values is representative of the LEMS population and was therefore considered in the base-case analysis." However, the sponsor identified inconsistencies when varying these estimates in probabilistic analysis, noting that the value for severe was better than that for asymptomatic in some cases. To avoid this problem, the sponsor performed a linear regression of the utilities for each severity category from MAHTA against the midpoint QMG score for each severity category (0.5 for asymptomatic, 4.5 for mild, 11.5 for moderate, and 27.5 for severe) and based the utilities actually used in the model on the fitted regression curve, varying only the slope and intercept values in probabilistic analysis (preserving the logical ordering across health states). The mean utility values used by the sponsor for each health state in the base-case analysis were:

- 0.79 for patients who were 'asymptomatic'
- 0.74 for patients in the 'mild' health state
- 0.66 for patients in the 'moderate' health state
- 0.48 for patients in the 'severe' health state.

Disutilities were applied for adverse events, but had a negligible impact on the sponsor's results.

Amifampridine costs $27.40 per 10 mg tablet. Therefore, the monthly cost of amifampridine in the sponsor's model depended upon dose, which in turn differed by health state:

- $3,336 per month for patients who were 'asymptomatic' (40 mg dose)
- $5,003 per month for patients in the 'mild' health state (60 mg dose)
- $6,671 per month for patients in the 'moderate' health state (80 mg dose)
- $8,339 per month for patients in the 'severe' health state (100 mg dose).

These monthly costs correspond to annual costs of $40,027 to $100,067, depending upon dose.

When provided alongside amifampridine, BSC was assumed to cost a total of:

- $31 per month for patients with ‘moderate’ primary autoimmune LEMS
- $465 per month for patients with ‘severe’ primary autoimmune LEMS
- $9 per month for patients with ‘moderate’ paraneoplastic LEMS
- $425 per month for patients with ‘severe’ paraneoplastic LEMS.

When provided as the comparator (without amifampridine), BSC was assumed to cost a total of:

- $34 per month for patients with ‘mild’ primary autoimmune LEMS
- $59 per month for patients with ‘moderate’ primary autoimmune LEMS
- $1,329 per month for patients with ‘severe’ primary autoimmune LEMS
- $12 per month for patients with ‘mild’ paraneoplastic LEMS
- $23 per month for patients with ‘moderate’ paraneoplastic LEMS
- $1,289 per month for patients with ‘severe’ paraneoplastic LEMS.

The additional cost of BSC when provided without amifampridine was driven by an assumed increase in the use of IVIg and plasma exchange.

The sponsor also modelled follow-up costs of $14 to $35 per month. Adverse-event costs were modelled, but had a negligible impact on the sponsor’s results.

Summary of Sponsor’s Economic Evaluation Results

The sponsor submitted probabilistic analyses (5,000 simulations).

Base-Case Results

In the sponsor’s base-case analysis, amifampridine + BSC was estimated to have a cost of $1,125,351 and a benefit of 10.25 QALYs, while BSC alone was estimated to have a cost of $167,275 and a benefit of 8.14 QALYs. As a result, the incremental cost of amifampridine + BSC was estimated to be $956,144, and the incremental QALYs were estimated to be 2.11 compared to BSC alone. This corresponded to an ICER of $453,809 per QALY.

The sponsor stated that changes in QMG score were assumed to have occurred within the first cycle of the model, representing the duration of effect found during the clinical trial. Only 0.55% of the QALYs with amifampridine + BSC were generated during this time (0.056 of 10.25 QALYs). Consequently, only 0.052% of the QALYs gained in the amifampridine arm were generated during the period of the trial (0.001 of 2.11 incremental QALYs). The sponsor reported a 0% probability that amifampridine + BSC is cost-effective, even at a WTP threshold of $200,000 per QALY.

No patients were still alive at the end of the time horizon (54 years). Beyond cycle 53 (4 years and 5 months), all patients still alive after receiving BSC alone were assumed to have worsened sufficiently to be in the severe health state (QMG > 16); beyond cycle 147 (12 years and 3 months), all such patients in the BSC-alone arm were assumed to have worsened to the point where their QMG score took the maximum possible value (QMG = 39). QMG scores did not worsen for patients receiving amifampridine + BSC, remaining stable over the model’s time horizon.

The submitted analysis was based on publicly available prices of the comparator treatments.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. BSC ($/QALY)
BSC alone	172,711	–	8.14	–	–
Amifampridine + BSC	1,128,855	956,144	10.25	2.11	453,809

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Note: Survival was equal in both arms of the model (incremental life-years gained = 0).

Source: Sponsor's pharmacoeconomic submission.

The sponsor reported both deterministic and probabilistic results, for which there were no important differences. The sponsor's probabilistic results are reported in Table 3.

Sensitivity and Scenario Analysis Results

The sponsor reported the following scenario analyses:

- societal perspective (ICER of $368,473 per QALY)
- 20-year time horizon (ICER of $471,106 per QALY)
- mean daily dose of 70 mg for every disease severity (ICER of $420,237 per QALY)
- cost of management of adverse events included (ICER of $455,112 per QALY)
- discount rate of 0% (ICER of $438,860 per QALY)
- discount rate of 3% (ICER of $470,412 per QALY).

Note that the probabilistic ICER remains in the range of $368,473 to $471,106 per QALY in each of these scenario analyses. Given the relatively small range of values, and how much higher all of these ICERs are than conventional WTP thresholds, no univariate change was considered influential enough to drive the analysis.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **QMG score is an inappropriate outcome measure for LEMS**: As noted in CADTH's clinical review, "[t]he QMG score is a 13-item, physician-assessed scale developed to assess patients with MG. Each parameter is measured on a 0- to 3-point scale (total score range: 0 to 39). The QMG is composed of the following items: ocular (2 items), facial (1 item), bulbar (2 items), gross motor (6 items), axial (1 item), and respiratory (1 item)."[9] The clinical review also noted that "[s]tudies validating the use of the QMG score in patients with LEMS were not identified in the literature" and that "the QMG score is not considered an appropriate or relevant assessment tool for LEMS, according to the clinical experts consulted by CADTH." Experts noted that few of the 13 items of the QMG are directly relevant for assessing the severity of LEMS, given that the characteristic symptoms of LEMS are related to leg weakness and difficulty walking. The clinical experts consulted by CADTH noted that the Triple-Timed Up-and-Go (3TUG) test is a more relevant measure for assessing LEMS. The clinical review team's finding that the QMG score is not considered an appropriate or relevant assessment tool for LEMS presents a fundamental problem for interpreting the results of the sponsor's economic evaluation, given that the health states used in the sponsor's model, the magnitude of treatment benefit with amifampridine + BSC, and the utilities used to calculate QALYs are all defined by or derived from QMG scores.

- Because the CADTH clinical review determined that QMG score is an inappropriate outcome measure for LEMS, the use of QMG in an economic model of LEMS is also inappropriate. Given that the sponsor's model is based on QMG scores, the relevance of the sponsor's results are unclear. CADTH was not able to address this limitation because numerous key components of the sponsor's model are based on QMG scores, including the categorization of patients into health states, the magnitude of treatment benefit with amifampridine + BSC, and the estimation of health utilities. The sponsor's model could not reflect outcomes using a different measure (such as 3TUG). A CADTH reanalysis was not conducted, given that it was not possible to produce reliable QALY estimates from changes in QMG score.

- **The sponsor's assumption of a degenerative course of LEMS on BSC is inappropriate**: The sponsor assumed no worsening of QMG scores over time for patients treated with amifampridine + BSC, yet assumed that QMG scores would worsen by 10% per annum for patients treated with BSC alone. This conflicts with the advice provided by the clinical experts consulted by CADTH, who did not consider LEMS to be degenerative. Furthermore, the sponsor's assumed rate of degeneration following treatment with BSC alone is so extreme that all 1,000 hypothetical patients in the sponsor's microsimulation (used to inform the transition probabilities for the state-transition model) were assumed to worsen from their starting health state (moderate) to the worst possible health state (severe) within 5 years. All 1,000 of these patients were also assumed to have the worst possible QMG score (a maximum score of 39) within 13 years. The clinical experts consulted by CADTH believed that this result lacked face validity.
  - Although no CADTH base-case reanalysis was performed (see first key limitation), CADTH conducted an exploratory analysis in which the only change from the sponsor's base-case assumptions was that the annual deterioration in QMG scores was assumed to be 0 for both amifampridine + BSC and BSC alone. The purpose of this analysis was to explore how sensitive the sponsor's base-case findings are to the assumption that QMG scores deteriorate following treatment with BSC alone. Note that the remaining limitations of the sponsor's base-case analysis also apply to this exploratory analysis.

- **Inappropriate use of discrete severity categories based on QMG score:** The sponsor categorized patients with LEMS into health states based on symptom severity, defined by QMG score. All patients in each category were then assigned the same health utility, derived from a linear regression carried out by the sponsor and based on the midpoint QMG score for the category in question. The clinical experts consulted by CADTH confirmed that QMG scores would be better considered on a continuum rather than within discrete categories. This use of discrete severity categories leads to inconsistencies in the calculation of health utilities: it can result in no changes in health utility following relatively large changes in QMG scores (e.g., a 6-point increase in a patient's QMG score, from 9 to 15, would not affect their health utility, given that the patient would remain in the moderate health state), while smaller changes in QMG scores can result in changes in health utility (e.g., a 2-point increase in a patient's QMG score, from 7 to 9, would reduce that patient's health utility because they would move from mild to moderate). The sponsor's inappropriate use of categorized health states based on QMG score also had implications for the estimated incremental cost of treatment because higher (and more costly) doses of amifampridine were assumed for patients in more severe health states.
  - Given that the model structure is based on this categorized approach, CADTH was unable to address this structural limitation.

- **Initial reduction in QMG score may not be clinically important:** In addition to the QMG score being an inappropriate outcome measure for LEMS (as discussed), the clinical review noted that the minimum clinically important difference (MCID) in QMG score for patients with MG is 2.6 points, and that no studies report a MCID in patients with LEMS. It follows that the initial 2.44-point reduction in QMG scores following

treatment with amifampridine + BSC modelled by the sponsor, based on the results from the Cochrane review, may not provide a meaningful clinical benefit to patients.

  - CADTH was not able to address this limitation because numerous key components of the sponsor's model are based on QMG scores (including the categorization of patients into health states, the magnitude of treatment benefit with amifampridine + BSC, and the estimation of health utilities). The sponsor's model was not programmed to allow for the use of other measures (e.g., 3TUG).

The following additional limitations were identified, but did not meaningfully affect results:

- **Inappropriate pooling of studies to derive a common baseline QMG score:** The sponsor derived a common baseline QMG score by pooling the results of 2 studies: Sanders (2000) and Oh (2009). The average QMG scores in these studies differ substantially (8.50 in Sanders and 13.00 in Oh). No attempt was made to adjust for differences between the populations of these 2 studies. Instead, the sponsor calculated a simple weighted average of the QMG scores across the 2 studies. This was not considered to be a key limitation because the baseline QMG score applies to both the treatment and the comparator, mitigating the impact of any issues in its derivation upon the incremental results of the analysis.
- **No evidence of effectiveness or cost-effectiveness in pediatric patients:** Although the indication includes patients 6 years of age and older, no pediatric evidence was submitted by the sponsor. Furthermore, the sponsor's submitted economic evaluation considered only adult patients, with an assumed age of 57 years in the base-case analysis, which was varied between 41 and 73 years in the sensitivity analysis. This was not considered a key limitation because the clinical experts consulted by CADTH advised that they would not expect to see any age-related difference in treatment effectiveness.

Additionally, the key assumptions shown in Table 4 were made by the sponsor and have been appraised by CADTH.

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted As Limitations to the Submission)

Sponsor's key assumption	CADTH comment
No difference in the effectiveness of treatment for patients with primary autoimmune or paraneoplastic LEMS.	The clinical experts consulted by CADTH considered this to be a reasonable assumption.

LEMS = Lambert-Eaton myasthenic syndrome.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

As noted previously, CADTH's clinical review found that, for LEMS, the QMG score is not applicable to use in Canadian clinical practice and "is not considered a relevant assessment tool by the clinical experts consulted by CADTH." This presents a fundamental problem, not only for interpreting the results of the sponsor's economic evaluation — given that the utilities used to calculate QALYs are derived from QMG scores — but also for conducting any reanalysis using the sponsor's model.

Given that the sponsor's model is driven by QMG scores, it was not feasible for CADTH to replace the QMG score with a more appropriate outcome measure. As a result, CADTH was unable to conduct any base-case reanalysis of the sponsor's model, given that any estimate of incremental effectiveness would be misleading.

Scenario Analysis Results

Because no reanalysis was performed, price-reduction analyses were conducted using the sponsor's base-case assumptions only. This deterministic analysis — based on publicly available prices of the comparator treatments and subject to the key limitations of the sponsor's model noted earlier — found that the price of amifampridine would need to be reduced by 76% for amifampridine + BSC to be cost-effective at a conventional threshold of $50,000 per QALY. It is important to keep in mind that this price-reduction estimate is based on estimates of incremental QALY that are likely not representative of the true effect of amifampridine treatment. Consequently, the true price reduction that would be needed for amifampridine to be cost-effective remains unknown. The directionality of bias within the sponsor's submission suggests that the price reduction would need to be higher than the sponsor's estimate.

CADTH also performed an exploratory analysis to determine how much of the sponsor's estimated incremental QALY benefit of 2.11 with amifampridine + BSC compared to BSC alone resulted from the sponsor's assumption that QMG scores would worsen by 10% per year for patients treated with BSC alone. CADTH ran the sponsor's model again using the sponsor's base-case assumptions, with the exception that the annual deterioration in QMG scores was assumed to be 0 for both amifampridine + BSC and BSC alone. This resulted in a 92% reduction in the incremental QALY benefit (a drop to 0.17 incremental QALYs from 2.11 incremental QALYs), which, in turn, increased the ICER to $6.4 million per QALY from $453,809 per QALY. An important implication of this exploratory analysis is that the 2.44-point average reduction in QMG scores with amifampridine + BSC modelled by the sponsor — which was based on the results of the Cochrane review by Keogh (2011) — explains no more than 8% of the incremental QALYs reported by the sponsor, with the remaining 92% of the incremental QALYs reported by the sponsor arising from the assumption that QMG scores would worsen by 10% per annum for patients treated with BSC alone.

Note that the remaining limitations of the sponsor's base-case analysis also apply to this exploratory analysis, and that this re-estimated incremental QALY benefit remains unlikely to be representative of the true effect of amifampridine treatment. (Further details of this exploratory analysis are provided in Appendix 4.)

Issues for Consideration

- Amifampridine has been used in the treatment of LEMS for many years, despite not having a Health Canada indication. The clinical experts consulted by CADTH suggested that access to the drug has been achieved through compassionate use programs or by patients paying out of pocket to a compounding pharmacy. The sponsor's estimate of amifampridine drug cost is substantially higher than what has been charged in the past. This high cost may be an insurmountable financial burden for many patients. Amifampridine is the only treatment that is formally indicated for LEMS.

Overall Conclusions

The sponsor submitted a model comparing treatment with amifampridine + BSC to BSC alone and reported a base-case ICER of $453,809 per QALY. This result suggests that, even under the sponsor's baseline assumptions, the probability that amifampridine is cost-effective is 0% at a WTP threshold of $50,000.

CADTH was not able to conduct a reanalysis due to foundational limitations within the sponsor's model and submitted evidence. The sponsor's model contained health states based on categories of disease severity based, in turn, on QMG scores. However, clinical experts and CADTH's clinical review agreed that QMG score is not an appropriate tool to measure LEMS severity. This means that the model's estimates of incremental QALY likely did not reflect the true impact of amifampridine treatment. Additionally, these QMG score categories produced a disproportionate change in health-state utility for patients at the margins, which was considered inappropriate, given that the QMG score is continuous. Finally, the baseline estimate of a 2.44-point reduction (improvement) in QMG score following treatment with amifampridine + BSC is below the threshold considered meaningful to patients, resulting in uncertainty about the true impact of treatment on health utility. These concerns arising from the outcome measure were compounded by additional concerns surrounding the validity of the model's assumptions about disease progression — assumptions that were responsible for the near entirety (92%) of the estimated incremental effectiveness. Collectively, these key limitations also severely limit the extent to which the sponsor's results can be interpreted. Due to these serious limitations with the submitted evidence, the incremental effectiveness of amifampridine is unknown. Consequently, a price reduction could not be estimated.

The use of the QMG score as the primary outcome measure raises the potential that meaningful benefits to patients may not have been captured by the sponsor's economic evaluation. It is possible that a more appropriate outcome measure (e.g., the 3TUG) would have captured any such benefits, providing a more informative estimate of the cost-effectiveness of treatment. A more robust estimate of treatment effectiveness would be particularly relevant, given that the cost of amifampridine treatment is considerable. (The sponsor's estimate of lifetime incremental cost was $956,144 per patient.)

Due to the methodological limitations identified within the model, the cost-effectiveness of amifampridine is unknown.

Appendix 1: Cost-Comparison Table

The comparators presented in Table 5 have been deemed appropriate based on feedback from clinical experts. Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table. As such, the table may not represent the actual costs to public drug plans.

Table 5: CADTH Cost-Comparison Table for Treatment of Lambert-Eaton Myasthenic Syndrome

Treatment	Strength	Form	Price ($)[a]	Body weight	Recommended dosage	Daily cost ($)	Annual cost ($)[b]
Amifampridine (Ruzurgi)	10 mg	Tablet	27.3973[a]	Less than 45 kg	40 mg daily	109.59	40,000
				More than 45 kg	80 mg to 100 mg daily	219.18 to 273.97	80,000 to 100,000

[a] Sponsor-submitted price.[1]

[b] Annual costs are based on 365 days per year.

Note: Pyridostigmine, immunosuppressants, intravenous immunoglobulin, and plasma exchange are occasionally used to manage symptoms in patients with LEMS, but are not formally indicated for disease treatment. Therefore, they were not considered comparators for the purpose of this table.

Appendix 2: Submission Quality

Table 6: Submission Quality

Description	Yes	No	Comments
Population is relevant, with no critical intervention missing and no relevant outcome missing.	☐	☒	The primary outcome measure (QMG score) used to determine health states and derive the utilities used to calculate QALYs was found by CADTH's clinical reviewers to be inappropriate for use in LEMS. Therefore, it is plausible that relevant benefits of treatment with the intervention are missing.
Model has been adequately programmed and has sufficient face validity.	☐	☒	The programming of the model is adequate, although there is evidence of poor practice (e.g., use of IFERROR functions). Some model assumptions lack face validity, such as the assumptions around worsening of QMG scores following treatment.
Model structure is adequate for decision problem.	☐	☒	The use of discrete ranges of QMG scores to define health states is inappropriate. A microsimulation model would have been more appropriate than a state-transition model, given uncertainty about the impacts of treatment across patients and the benefits of considering such impacts on a continuum.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis).	☐	☒	The common baseline QMG scores were calculated using an inappropriate method that did not account for patient heterogeneity between studies.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem.	☐	☒	The probability that the intervention was cost-effective was reported at an unjustifiably high threshold of $200,000 per QALY. Structural uncertainty was not adequately considered.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details).	☒	☐	The report was adequately organized and sufficiently transparent, with enough technical detail reported.

LEMS = Lambert-Eaton myasthenic syndrome; QALY = quality-adjusted life-year; QMG = quantitative myasthenia gravis.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Table 7: Disaggregated Summary of the Sponsor's Economic Evaluation Results

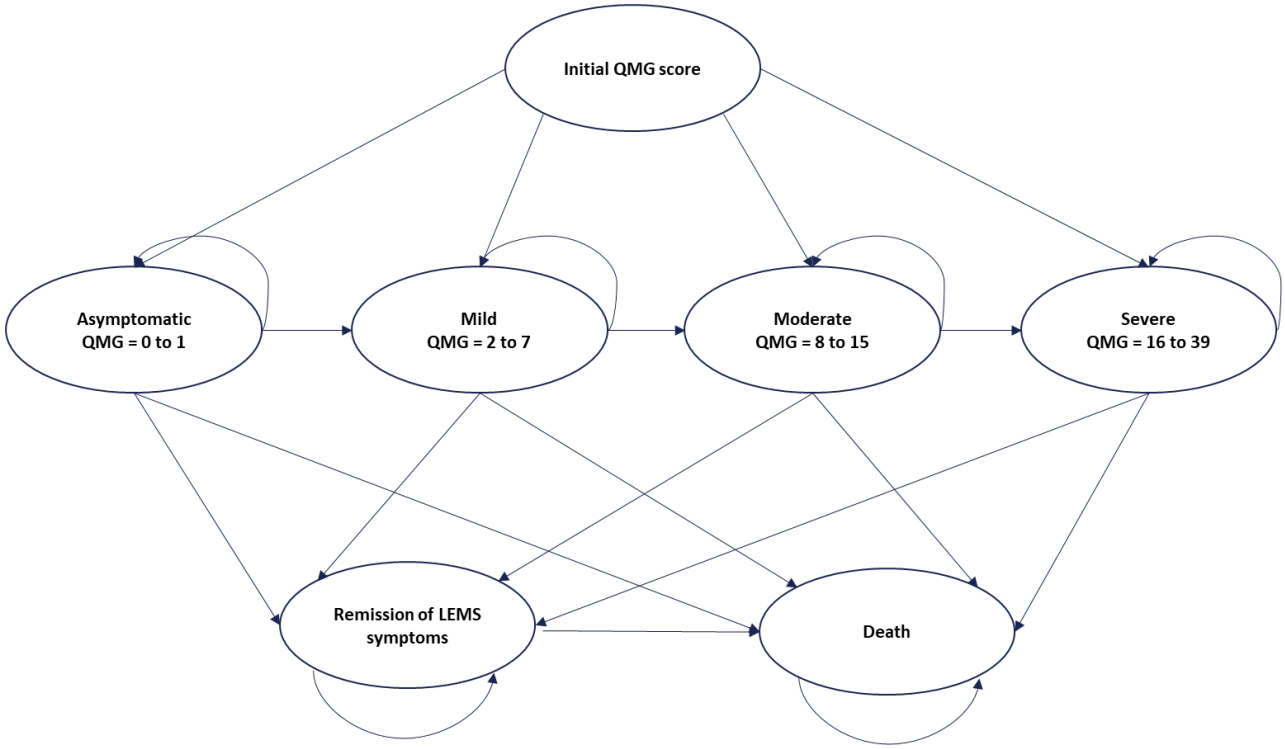
Parameter	Amifampridine + BSC	BSC alone	Incremental
Discounted LYs			
Total	18.93[a]	18.93[a]	0.00
Remission	2.78	2.78	0.00
Asymptomatic	0.00	0.00	0.00
Mild	2.61	2.61	0.00
Moderate	13.54	13.54	0.00
Severe	0.00	0.00	0.00
Discounted QALYs			
Total	10.25	8.14	2.11
Remission	1.41	1.41	0.00
Asymptomatic	0.00	0.00	0.00
Mild	1.57	0.00	1.57
Moderate	7.26	1.80	5.46
Severe	0.00	4.93	–4.93
Discounted costs ($)			
Total	$1,128,855	$172,711	$956,144
Drug cost	$1,125,351	$167,275	$958,076
Follow-up	$3,505	$5,436	–$1,931
Adverse events	$0	$0	$0
Indirect costs	$0	$0	$0
ICER ($/QALY)	$453,809		

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year.

[a] The total LYs for both strategies reported in the sponsor's report was 48.19, which erroneously included 29.27 LYs in the dead state. The total LYs reported in this table were re-calculated by CADTH, based on the LYs reported for the alive states only.

Source: Sponsor's pharmacoeconomic submission, Table 23.[1]

Figure 1: Model Structure



LEMS = Lambert-Eaton myasthenic syndrome; QMG = quantitative myasthenia gravis.

Source: Sponsor's pharmacoeconomic submission, Figure 4.[1]

The baseline characteristics of the target population in the sponsor's model are reproduced in Table 8.

Table 8: Baseline Characteristics of the Target Population

Patient parameter	Value	SD	Source
Age (years)	56.9	16.1	Weighted average of Sanders (2000)[3] and Oh (2009)[6]
Proportion of females (%)	47%	–	Weighted average of Sanders (2000)[3] and Oh (2009)[6]
Body weight (kg)	78.3	19.4	Sanders (2018)[11]
Proportion of paraneoplastic LEMS (%)	39%	–	Weighted average of Sanders (2000)[3] and Oh (2009)[6]

LEMS = Lambert-Eaton myasthenic syndrome; SD = standard deviation.

Source: Sponsor's pharmacoeconomic submission, Table 1.[1]

The values used to calculate the common baseline QMG score in the sponsor's model are reproduced in Table 9.

Table 9: Common Baseline QMG Scores

Source	Amifampridine + BSC			BSC alone		
	N	Average QMG score	SD	N	Average QMG score	SD
Sanders (2000)	12	8.50	7.19	14	12.30	3.34
Oh (2009)	6	13.00	2.65	6	13.00	2.65
Total	18	10.00	5.68	20	12.51	3.13
Common baseline QMG score (weighted average)	**–**	**11.32**	**4.34**	**–**	**11.32**	**4.34**

BSC = best supportive care; QMG = quantitative myasthenia gravis; SD = standard deviation.

Note: "3,4-DAP + BSC" in the sponsor's table has been replaced with "amifampridine + BSC" here; and "placebo + BSC" in the sponsor's table has been replaced with "BSC alone" here to ensure consistency with the remainder of this report.

Source: Sponsor's pharmacoeconomic submission, Table 2.[1]

The initial health states in which patients begin the sponsor's model (prior to worsening) are reproduced in Table 10.

Table 10: Proportion of Population in Each Health State (Prior to Worsening)

Treatment	Asymptomatic (QMG = 0 to 1)	Mild (QMG = 2 to 7)	Moderate (QMG = 8 to 15)	Severe (QMG = 16 to 39)
Amifampridine + BSC	0%	7.6%	92.4%	0%
BSC alone	0%	0%	100%	0%

BSC = best supportive care; QMG = quantitative myasthenia gravis.

Note: "3,4-DAP + BSC" in the sponsor's table has been replaced with "amifampridine + BSC" here; and "placebo + BSC" in the sponsor's table has been replaced with "BSC alone" here to ensure consistency with the remainder of this report. Furthermore, the category boundaries have been corrected from those reported in the sponsor's table.

Source: Sponsor's pharmacoeconomic submission, Table 4.[1]

The health-state utility values used by the sponsor are reproduced in Table 11. The regression analysis used to inform these values is reproduced in Figure 2.

Table 11: Health-State Utility Values

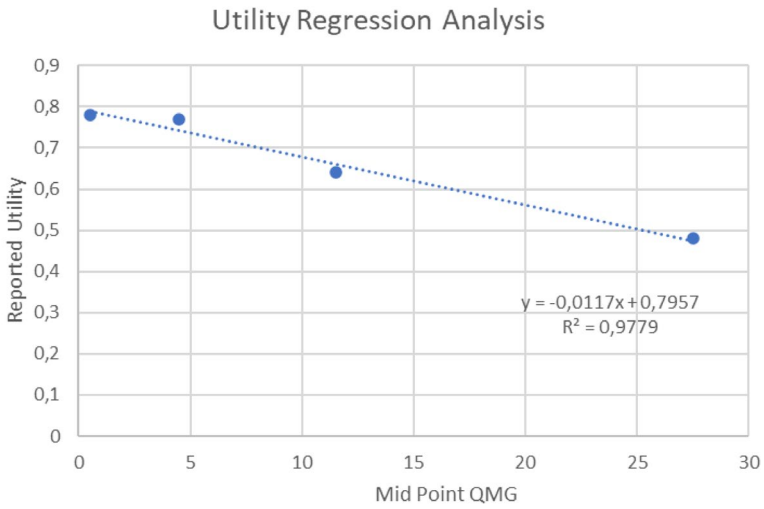
Health state	Midpoint QMG score	Reported utility value	Used utility value[a]	Source
Asymptomatic (QMG = 0 to 1)	0.5	0.78	0.79	MAHTA (2018)[7] expert opinion
Mild (QMG = 2 to 7)	4.5	0.77	0.74	
Moderate (QMG = 8 to 15)	11.5	0.64	0.66	
Severe (QMG = 16 to 39)	27.5	0.48	0.48	

QMG = quantitative myasthenia gravis.

[a] Derived from the regression analysis.

Source: Sponsor's pharmacoeconomic submission, Table 7.[1]

Figure 2: Regression Analysis for Utility Values



Source: Sponsor's pharmacoeconomic submission, Figure 7.[1]

The unit costs associated with BSC are reproduced in Table 12.

Table 12: Unit Costs of Best Supportive Care

Treatment	Unit cost	Dosage form	Recommended dose	Monthly frequency	Monthly cost	Source
Pyridostigmine	**$1.1920**	**180 mg**	**229 mg daily**	**Daily**	**$46.16**	ODB Formulary[12] Sanders (2018)[11] Furlan (2016)[13] Statistics Canada[14] Expert opinion
Immunosuppressants (average)	-	-	-	-	$44.35	
Azathioprine	$0.2405	50 mg	3 mg/kg daily	Daily	$34.39	
Mycophenolate	$0.3712	250 mg	2,000 mg daily	Daily	$90.39	
Prednisone	$0.1735	50 mg	1 mg/kg daily	Daily	$8.27	
IVIg	$9,057	–	–	Every 3 months	$3,019	
PLEX	$6,835	–	–	Every 6 months	$1,139	

IVIg = intravenous immunoglobulin; ODB = Ontario Drug Benefit; PLEX = plasma exchange.

Source: Sponsor's pharmacoeconomic submission, Table 11.[1]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Detailed Results of CADTH Base Case

The CADTH clinical review found that, for LEMS, the QMG score is not applicable to use in Canadian clinical practice and "is not considered a relevant assessment tool by the clinical experts consulted by CADTH." This not only presents a fundamental problem for interpreting the results of the sponsor's economic evaluation — given that the utilities used to calculate QALYs are derived from QMG scores — but also for conducting any reanalysis using the sponsor's model.

Given the dependency of the sponsor's model on the consideration of QMG scores, it was not feasible for CADTH to replace the QMG score with a more appropriate outcome measure. Therefore, the economic review team decided not to perform any base-case reanalysis of the sponsor's model, given that any estimate of incremental effectiveness would be misleading.

Price-Reduction Analysis

Because no reanalysis was performed, price-reduction analyses were conducted using only the sponsor's base-case assumptions (Table 13). These deterministic analyses — based on publicly available prices of the comparator treatments and subject to the key limitations of the sponsor's model noted earlier — found that the price of amifampridine would need to be reduced by 76% for amifampridine + BSC to be cost-effective at a conventional threshold of $50,000 per QALY. It is important to recognize that this price-reduction analysis is based on estimates of incremental QALY that are likely not representative of the true effect of amifampridine treatment. Consequently, the true price reduction that would be needed for amifampridine to be cost-effective remains unknown. The directionality of bias within the sponsor's submission suggests that the price reduction would need to be higher than the sponsor's estimate. Details of the price-reduction analysis using the sponsor's submitted evidence are provided in Appendix 4.

Table 13: Price-Reduction Analyses of Sponsor's Base Case

	ICERs for amifampridine + BSC vs. BSC alone	
Price reduction	**Sponsor's base case**	**CADTH reanalysis**
No price reduction	$472,276	NA[a]
10%	$416,871	NA
20%	$361,466	NA
30%	$306,060	NA
40%	$250,655	NA
50%	$195,249	NA
60%	$139,844	NA
70%	$84,438	NA
76%	**$49,533**	NA
80%	$29,033	NA

	ICERs for amifampridine + BSC vs. BSC alone	
Price reduction	Sponsor's base case	CADTH reanalysis
90%	Dominant	NA

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; NA = not applicable; vs. = versus.

[a] CADTH did not conduct reanalysis due to limitations within the sponsor's model.

Note: All analyses in this table are deterministic.

Scenario Analyses

Although CADTH did not conduct any formal reanalyses of the sponsor's model, the economic review team performed an exploratory analysis to determine how much of the sponsor's estimated incremental QALY benefit of 2.11 with amifampridine + BSC compared to BSC alone resulted from the assumption that QMG scores would worsen by 10% per year for patients treated with BSC alone.

This analysis was performed by modifying a single cell in the sponsor's submitted economic model, in which the sponsor had entered the assumed 10% annual deterioration in QMG score for patients treated with BSC alone. The economic review team modified this value to 0%, but retained all other assumptions from the sponsor's base-case analysis. A probabilistic analysis (5,000 simulations) was then conducted.

This resulted in a substantial increase in the total QALYs for BSC alone (to 10.10 QALYs from 8.14 QALYs), and a substantial reduction in the total costs of BSC alone (to $13,237 from $172,711) (Table 14). Minor changes in total costs and total QALYs were observed for amifampridine + BSC; these can be attributed to Monte Carlo error, given that changing cell D36 has no impact on the amifampridine + BSC strategy. The increased total QALYs and reduced total costs with BSC alone resulted in a 92% reduction in the incremental QALY benefit of amifampridine + BSC compared to BSC alone (to 0.17 incremental QALYs from 2.11 QALYs) and a 17% increase in incremental costs (to $1,115,289 from $956,144). This, in turn, resulted in a 13-fold increase in the ICER for amifampridine + BSC compared to BSC alone: from $453,809 per QALY in the sponsor's base-case submission to $6.4 million per QALY in this exploratory analysis.

It should be noted that this reported ICER ($6.4 million per QALY, arising from the probabilistic exploratory analysis) differed substantially from that which would have arisen from a *deterministic* exploratory analysis. Had the exploratory analysis been deterministic, the incremental cost would have been higher ($1,150,511 instead of $1,115,289) and the incremental QALYs lower (0.08 instead of 0.17), resulting in an ICER more than double that in the probabilistic exploratory analysis reported earlier ($13.8 million per QALY instead of $6.4 million per QALY). This much higher deterministic ICER is driven by the proportionately smaller incremental QALYs in the deterministic analysis (i.e., 0.08 is less than half 0.17), despite the *absolute* difference in incremental QALYs between the probabilistic and deterministic analyses being small. In net monetary benefit terms, the difference in incremental QALYs between the probabilistic and deterministic analyses is just $4,500, assuming a WTP threshold of $50,000 per QALY. Therefore, it is important not to attribute too much significance to the absolute difference in the ICER between the probabilistic and deterministic exploratory analyses, given that, in net monetary benefit terms, the results of these analyses are similar.

An implication of this exploratory analysis is that the sponsor's assumed 2.44-point average reduction in QMG scores with amifampridine + BSC explains no more than 8% of the

incremental QALYs reported by the sponsor, with the remaining 92% of incremental QALYs attributable to the sponsor's assumption that QMG scores would worsen by 10% per year for patients treated with BSC alone. This is important to note because the results of the Cochrane review by Keogh (2011), which were used to inform the initial 2.44-point average improvement in QMG scores with amifampridine + BSC, can explain no more than 8% of the incremental QALYs reported by the sponsor. By contrast, the sponsor's assumed 10% annual worsening in QMG scores with BSC alone — which was unsupported by evidence — is responsible for 92% of the reported incremental QALYs.

It should be noted that the remaining key limitations of the sponsor's base-case analysis noted earlier also apply to this exploratory analysis, including the fundamental limitation that the model is based on a consideration of QMG scores. Therefore, this exploratory analysis should not be interpretated as a formal CADTH reanalysis in which credence should be given to the results; in particular, the incremental QALY benefit estimated as part of this exploratory analysis remains unlikely to be representative of the true effect of amifampridine treatment, such that the corresponding ICER is unlikely to be reflective of the true cost-effectiveness of amifampridine. Instead, the key insight from this exploratory analysis is that a key assumption within the sponsor's base-case analysis substantially biased the analysis in favour of amifampridine.

Table 14: Summary of CADTH Exploratory Analysis

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. BSC ($/QALY)
BSC alone	13,237	–	10.10	–	–
Amifampridine + BSC	1,128,526	1,115,289	10.27	0.17	6,435,018

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; vs. = versus.

Source: Probabilistic exploratory analysis of the sponsor's pharmacoeconomic submission.[1]

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Key Take-Aways of the Budget Impact Analysis

- CADTH identified the following key limitations with the sponsor's analysis:
  - Patients with primary autoimmune LEMS were assumed to be older than suggested by clinical evidence and expert opinion.
  - The daily dose of amifampridine was assumed to be 70 mg without consideration of the different doses recommended in the product monograph.
- The CADTH reanalysis corrected the age breakdown for patients with primary autoimmune LEMS. Based on the CADTH base case, the budget impact is expected to be $3,942,075 in year 1, $4,364,043 in year 2, and $4,658,441 in year 3, for a 3-year budget impact $12,964,559.
- CADTH found the budget impact to be sensitive to the assumed daily dose of amifampridine.

Summary of Sponsor's Budget Impact Analysis

The submitted budget impact analysis (BIA) assessed the introduction of amifampridine for the treatment of patients 6 years of age or older with LEMS. The analysis was undertaken from a drug plan perspective using an epidemiologic approach, with drug acquisition costs as well as dispensing fees and markups considered. A 3-year time horizon was used, from 2021 to 2023, with 2020 as the base year. The prevalence and incidence of LEMS were estimated to be 2.3 per million and 0.5 per million, respectively.[15] Of the incident cases, 57% were assumed to be associated with a cancer, while 43% of cases were generally primary autoimmune.[8] All of the prevalent cases were assumed to be primary autoimmune LEMS due to the poor survival of patients with paraneoplastic LEMS. All patients with paraneoplastic LEMS were assumed to be seniors 65 years or older with an estimated public drug coverage rate of 90.6%.[16] Of the patients with primary autoimmune LEMS, 50% were assumed to be younger than 65 years, and 50% were assumed to be 65 years or older. The drug coverage rate was 30.9% for those under 65 years.

No comparators were identified by the sponsor as being relevant to the review, with many of the usual treatments for LEMS being used off-label. The reference scenario included only BSC; the new drug scenario included amifampridine, which was assumed to capture 100% of the market share. Key inputs to the BIA are documented in Table 15.

Table 15: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1/year 2/year 3 if appropriate)
Target population	
Canadian population in 2019	29,104,297
Annual growth of Canadian population	1.23%[17]
Incidence of LEMS	0.00005%[15]
Prevalence of LEMS	0.00023%[15]
Paraneoplastic LEMS	
Proportion incident LEMS that is paraneoplastic	57.0%[8]
Proportion prevalent LEMS that is paraneoplastic	0%

Parameter	Sponsor's estimate (reported as year 1/year 2/year 3 if appropriate)
Proportion < 65 years old	0%
Proportion ≥ 65 years old	100%
Primary autoimmune LEMS	
Proportion incident LEMS that is primary autoimmune	43.0%[8]
Proportion prevalent LEMS that is primary autoimmune	100%
Proportion < 65 years old	50%
Proportion ≥ 65 years old	50%
Coverage	
Public drug coverage < 65 years old	30.9%[16]
Public drug coverage ≥ 65 years old	90.6%[16]
Number of patients eligible for the drug under review	64/70/75
Market uptake (3 years)	
Uptake (reference scenario) Best supportive care	100%/100%/100%
Uptake (new drug scenario) Amifampridine	100%/100%/100%
Cost of treatment (per patient)	
Cost of annual treatment Amifampridine (70 mg daily) Best supportive care	$70,046 $0

LEMS = Lambert-Eaton myasthenic syndrome.

Summary of the Sponsor's Budget Impact Analysis Results

The estimated budget impact of funding amifampridine for the treatment of LEMS was expected to be $4,695,503 in year 1, $5,178,257 in year 2, and $5,534,213 in year 3, for a total of $15,407,973 over the 3-year time horizon.

CADTH Appraisal of the Sponsor's Budget Impact Analysis

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the results of the BIA.

- **Age assumptions in primary autoimmune LEMS:** The sponsor assumed that the split for patients with primary autoimmune LEMS who were under 65 years old and 65 years or older would be 50% each. This has implications for the proportion of patients being covered by public drug programs because the proportions differ between these 2 age groups. Based on the younger mean age in the DAPPER trial, CADTH assumed that 70% of patients with primary autoimmune LEMS would be under 65 years old and 30% would be 65 years or older.[11] These estimates were confirmed by the clinical experts consulted by CADTH for this review, who estimated that most patients with primary autoimmune LEMS would be under 65 years.
    - CADTH changed the age distribution of patients with primary autoimmune LEMS to be 70% for those under 65 years and 30% for those 65 years or older as part of the base case.

- **Simplistic dosing assumptions:** The sponsor assumed that all patients considered in the BIA would receive, on average, 70 mg of amifampridine per day. However, the product monograph for amifampridine recommends differential dosing based on patient weight (< 45 kg and ≥ 45 kg) as well as a range of recommended daily doses, from 80 mg to 100 mg for patients weighing greater than or equal to 45 kg.[18] The clinical experts consulted by CADTH emphasized that the dose would likely depend on symptom severity and would differ between patients. To incorporate this into the model, the sponsor would have had to include the functionality to subdivide patients based on weight and symptom severity. However, due to structural limitations, CADTH was not able to address this in the base case.
  - CADTH explored the effect of changing the daily dose of amifampridine as part of its scenario analyses.

CADTH noted a slight discrepancy between the submitted price of amifampridine and the price used in the BIA model. This was corrected as part of the base case.

CADTH Reanalyses of the Budget Impact Analysis

Based on the limitations identified, CADTH's base case included the corrected value for the drug price as well as a change to the age distribution of patients with primary autoimmune LEMS (Table 16).

Table 16: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Correction to the price of amifampridine in the submitted BIA model	$27.397 per 10 mg tablet	$27.397**3** per 10 mg tablet
Changes to derive the CADTH base case		
1. Age assumptions in patients with primary autoimmune LEMS	50% assumed to be < 65 years old 50% assumed to be ≥ 65 years old	70% assumed to be < 65 years old 30% assumed to be ≥ 65 years old
CADTH base case		Reanalysis 1

The results of the CADTH step-wise reanalysis are presented in summary format in Table 17, and a more detailed breakdown is presented in Table 18. Based on the CADTH base case, the expected budget impact of the reimbursement of amifampridine for patients with LEMS is expected to be $3,942,075 in year 1, $4,364,043 in year 2, $4,658,441 in year 3, for a 3-year budget impact $12,964,559.

Scenario analyses involving the daily dose of amifampridine were conducted using the CADTH base case. The 3-year budget impact increased to $14,802,266 and $16,639,973 when daily doses of 80 mg and 90 mg were assumed, respectively. CADTH found the budget impact to be sensitive to assumptions about the daily dose of amifampridine, which was consistent with the sponsor's sensitivity analyses.

Table 17: Summary of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	3-year total
Submitted base case	$15,407,973
CADTH reanalysis 1/**CADTH base case**	**$12,964,559**

Table 18: Detailed Breakdown of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	Scenario	Year 1	Year 2	Year 3	3-year total
Submitted base case	Reference	$0	$0	$0	$0
	New drug	$4,695,503	$5,178,257	$5,534,213	$15,407,973
	Budget impact	**$4,695,503**	**$5,178,257**	**$5,534,213**	**$15,407,973**
CADTH base case	Reference	$0	$0	$0	$0
	New drug	$3,942,075	$4,364,043	$4,658,441	$12,964,559
	Budget impact	**$3,942,075**	**$4,364,043**	**$4,658,441**	**$12,964,559**
CADTH scenario analysis 1a: 80 mg daily amifampridine	Reference	$0	$0	$0	$0
	New drug	$4,500,863	$4,982,640	$5,318,764	$14,802,266
	Budget impact	**$4,500,863**	**$4,982,640**	**$5,318,764**	**$14,802,266**
CADTH scenario analysis 1b: 90 mg daily amifampridine	Reference	$0	$0	$0	$0
	New drug	$5,059,650	$5,601,236	$5,979,087	$16,639,973
	Budget impact	**$5,059,650**	**$5,601,236**	**$5,979,087**	**$16,639,973**
CADTH scenario analysis 2: 76.3% price reduction	Reference	$0	$0	$0	$0
	New drug	$957,980	$1,060,549	$1,132,112	$3,150,640
	Budget impact	**$957,980**	**$1,060,549**	**$1,132,112**	**$3,150,640**

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