CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

Final

Amifampridine (Ruzurgi)

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

Recommendation: Reimburse with conditions

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Single Technology

What is the CADTH reimbursement recommendation for Ruzurgi?

CADTH recommends that Ruzurgi should be reimbursed by public drug plans for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 years of age and older only if certain conditions are met.

What are the conditions for reimbursement?

Ruzurgi should only be reimbursed if it is prescribed by a neurologist and if the cost of the medication is reduced.

Which patients are eligible for coverage?

All patients with LEMS who are 6 years of age or older should be eligible for treatment with Ruzurgi for at least 3 months before assessing whether they respond to treatment.

Why did CADTH make this recommendation?

One clinical trial showed that patients who continued to receive treatment with Ruzurgi had less disability progression than patients who stopped treatment. Although the true cost-effectiveness of Ruzurgi is unclear, the price of Ruzurgi needs to be at least 76% lower to make it more cost-effective. Reimbursing Ruzurgi at the price submitted by the sponsor would cost approximately $13,000,000 over 3 years.

Key Messages

- Clinical evidence suggests that Ruzurgi reduces disability progression in patients with LEMS.
- Ruzurgi is not cost-effective and reimbursement would cost public drug plans approximately $13,000,000 over 3 years at the price submitted by the sponsor.
- The price would need to be reduced by at least 76% to improve its cost-effectiveness and make it more affordable for public payers.
- If the price of Ruzurgi is not reduced to a point that is affordable to public payers, this could delay access to the only treatment that has been approved for LEMS in Canada.

What is LEMS?

LEMS is a rare disease where the immune system attacks the body's own connections between nerves and muscles. Symptoms include muscle weakness in the legs and hips and reduced reflexes. As LEMS progresses, patients may experience weakness in the arms, swallowing difficulties, slurred speech, neck weakness, double vision, and droopy eyes. Fewer than 1 new case of LEMS is diagnosed per 2 million people each year.

What is Ruzurgi?

Ruzurgi (amifampridine) is approved by Health Canada for the symptomatic treatment of LEMS in patients 6 years of age and older. It is not known exactly how amifampridine works, but it reduces muscles weakness that occurs in patients with LEMS. Ruzurgi is a pill that is taken by mouth with or without food.

How much does Ruzurgi cost?

Ruzurgi is very expensive and is expected to cost between $40,000 and $100,000 per patient, per year, depending on the weight of the patient.

What other treatments are available for LEMS?

There are no other treatments approved to treat LEMS in Canada. Pyridostigmine may be used to improve muscle weakness, but it is not very effective and is usually used in patients who are waiting for treatment with amifampridine.

Unmet Needs in LEMS

Amifampridine has been used for the treatment of LEMS for many years through Health Canada's Special Access Programme or by being provided on compassionate grounds by the manufacturer. This was because amifampridine was not commercially available in Canada. As of August, 2020, amifampridine was approved for sale in Canada. As a result, it will no longer be available through the Special Access Programme. For access to amifampridine to be provided through publicly funded drug plans, amifampridine must be reviewed by CADTH.

AMIFAMPRIDINE (RUZURGI — MÉDUNIK CANADA INC.)

Therapeutic Area: Lambert-Eaton myasthenic syndrome (LEMS)

Recommendation

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

Rationale for the Recommendation

One phase II randomized, double-blind, placebo-controlled study (DAPPER, N = 32) demonstrated that continuous treatment with amifampridine was associated with a reduction in disability progression compared with patients from whom amifampridine was withdrawn. None of the patients who received continuous amifampridine exhibited a deterioration of 30% or more on the Triple Timed Up and Go (3TUG) test; whereas, 72% of patients deteriorated after the withdrawal of amifampridine; this difference was statistically significant ($P < 0.0001$). The effect of amifampridine on health-related quality of life (HRQoL) and productivity was not evaluated in the DAPPER study and remains unknown.

The sponsor's submitted price of amifampridine is $27.40 per 10 mg tablet. The recommended dose of amifampridine depends on body weight; therefore, the average daily treatment cost ranges from $109.59 to $273.97, while the average annual cost of treatment is between $40,000 and $100,000 per patient. Limitations of the clinical data and methodological issues within the sponsor's economic model prevented an accurate estimation of the cost-effectiveness of amifampridine. The sponsor estimated an incremental cost-effectiveness ratio (ICER) of $453,809; however, CDEC concluded that this value likely does not reflect the true cost-effectiveness of amifampridine compared to best supportive care (BSC). According to the sponsor's base case, there was 0% probability that amifampridine is cost-effective compared to BSC at a $50,000 per quality-adjusted life-year (QALY) willingness-to-pay (WTP) threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Patients with LEMS who are 6 years of age and older.	The Heath Canada indication specifies that amifampridine is only to be used in patients 6 years of age and older.
Renewal	
1. Patients should be assessed for a response to treatment within 3 months of initiating amifampridine. 1.1. A response to treatment is defined as an improvement of at least 30% on the 3TUG test.	Based on input from clinical experts, titration to the optimal effective dose requires between 2 and 3 months. In the DAPPER study, disability progression was assessed using the 3TUG test, where a > 30% deterioration in 3TUG time was considered to be clinically relevant.
Prescribing	
1. 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.
Pricing	
1. Reduction in price.	Although the true ICER is unknown, a price reduction of at least 76% would be required to improve the cost-effectiveness of amifampridine to a level that would be more acceptable to public payers.

3TUG = Triple Timed Up and Go; ICER = incremental cost-effectiveness ratio; LEMS = Lambert-Eaton myasthenic syndrome.

Implementation Guidance

1. 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.
2. 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.

Discussion Points

- CDEC heard from clinical experts that amifampridine had been previously 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 effective alternative treatment options are currently available. Since amifampridine is now marketed in Canada, it will no longer be available through SAP.
- CDEC discussed that all patients with LEMS who are 6 years of age or older should be eligible for a trial with amifampridine, as per the Health Canada approved indication. 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.
- Antibody tests (against the P/Q type voltage-gated calcium channels) may be used to confirm the diagnosis of LEMS, but these tests may not be readily available. CDEC discussed that the need for a confirmatory diagnostic test should be determined by the treating physician.

- The 3TUG test was used to assess disability progression in the DAPPER study and clinical experts consider this to be a clinically relevant tool and an appropriate assessment of function in patients with LEMS. A 30% improvement on the 3TUG test was considered an appropriate threshold to determine a response to treatment with amifampridine based on the definition of deterioration used in the DAPPER trial.
- Patients who respond to treatment with amifampridine are expected to continue treatment throughout their life. According to clinical experts, it is unlikely that patients who exhibit an initial response to treatment will stop responding. There was no evidence in the DAPPER trial to inform the duration of response to treatment with amifampridine.
- CDEC recognized that other LEMS-related treatments may be used in addition to amifampridine in some patients. In the DAPPER study, concomitant treatment with pyridostigmine, immunomodulators/immunosuppressants, or steroids was permitted in patients who received stable doses of these drugs for 3 months before entry in the study.
- Structural and methodological limitations within the sponsor's pharmacoeconomic model made CADTH's estimate of cost-effectiveness highly uncertain. In addition to using the Quantitative Myasthenia Gravis (QMG) score (which is not considered to be an appropriate or relevant assessment tool for LEMS by clinical experts) as an outcome measure, the sponsor's model was predominantly driven by an assumption about changing disease severity that lacked face validity or empirical support. Estimates of the price reduction and ICER should be interpreted with caution.

Background

Amifampridine has been used as a first line of therapy for both paraneoplastic and primary autoimmune forms of LEMS in Canada for many years despite it not being commercially available in Canada until 2020. Amifampridine has historically been accessed through Health Canada's SAP or through compassionate use by the sponsor.

Amifampridine has a Health Canada indication for the symptomatic treatment of LEMS in patients 6 years of age and older. Amifampridine is a broad-spectrum potassium channel blocker. It is available as 10 mg tablets. Dosing of amifampridine should be individualized based on disease severity and patient response and should be gradually titrated to the optimal effective dose with the minimum of side effects. The Health Canada recommended maximum total daily maintenance dose for patients weighing less than 45 kg is 40 mg. For patients weighing 45 kg or more the maximum total daily maintenance dose of amifampridine is 80 mg.

Summary of Evidence

To make their recommendation, CDEC considered the following information:

- a systematic review that included 1 phase II RCT in adult patients with LEMS
- a testimonial describing the experience of 1 Canadian patient with LEMS
- input from 2 clinical specialists with expertise diagnosing and treating patients with LEMS
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Summary of Patient Input

No patient group input was received for this review; a testimonial of the experiences of 1 Canadian patient 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 prone to falls. 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 pyridostigmine had no effect; however, 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) with a return to almost normal capabilities.

- The patient testimonial highlighted both the desire for improvement in muscle strength and bodily functions with the goal of performing daily activities with a sense of normalcy, and concern regarding the unaffordable price of amifampridine.

Clinical Trials

The CADTH systematic review included 1 phase II, double-blind, placebo-controlled withdrawal study (DAPPER; N = 32). DAPPER aimed to confirm the safety and evaluate the efficacy of amifampridine for the treatment of weakness associated with LEMS in adult patients. Patients with known clinically active LEMS who had continuous, stable use of amifampridine for at least 3 months were enrolled in the study. Patients on other LEMS-related treatments (in addition to amifampridine) were required to be on a stable regimen for at least 3 months. Patients were required to be responsive to amifampridine, defined as being able to experience an unequivocal improvement in a LEMS-induced dysfunction within 15 to 30 minutes after they took their first dose of amifampridine in the morning. Patients were excluded from DAPPER if they did not display a sufficiently large response to amifampridine during the baseline observation period.

DAPPER was composed of 3 stages. Stage I involved 2 days of baseline assessments to determine response to amifampridine. Patients who had sufficient response to amifampridine as indicated by the 3TUG and were eligible for enrolment in DAPPER, entered stage II where they were centrally randomized in a 1:1 ratio to continue their current amifampridine treatment regimen (Group A, continuous amifampridine) or to withdraw from amifampridine (Group B, taper to placebo) for up to 3.5 days. Patients in the placebo arm had their baseline amifampridine tapered over a 72-hour period followed by approximately 16 hours of placebo with no amifampridine. Baseline amifampridine was restored during stage III where patients were observed for half a day or until clinically stable.

No patients discontinued from the study; however, more patients in the taper to placebo arm (44.4%) compared to patients treated with continuous amifampridine (14.3%) had early entry to stage III of the trial where baseline amifampridine was reinstated.

The key limitations of the phase II study, DAPPER, related to internal validity issues such as the increased potential for unblinding and descriptive assessment of outcomes, and generalizability issues. The study population consisted of patients who were treatment-experienced and responsive to amifampridine at baseline, therefore, the magnitude of the treatment response observed in DAPPER may not be representative of the Canadian amifampridine-experienced population and may not generalizable to amifampridine-naive patients, including those who are newly diagnosed with LEMS.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, CDEC discussed the following: 3TUG test, Subject Self-Assessment of LEMS-Related Weakness (W-SAS), compound muscle action potential (CMAP), Lower Extremity Function Scale (LEFS), and LEMS-related activities of daily living (ADLs).

Disability Progression

Triple Timed Up and Go test (3TUG): The 3TUG test is a non-invasive measure of disease severity in patients with LEMS. The 3TUG consists of 3 consecutive laps where the patient rises from a straight-backed chair, walks 3 metres, and returns to the chair. The 3TUG time is the average of the 3 lap times. Higher 3TUG scores represent greater impairment. In DAPPER, the 3TUG was assessed according to the following 7 categories from A to G: A > 30% faster; B 30% slower to 30% faster; C > 30% to 50% slower; D > 50% to 100% slower; E > 100% to 200% slower; F > 200% slower; G cannot perform 3TUG. In an assessment of validity, the a priori acceptable range was < 20% difference in 3TUG times and a coverage probability (CP) ≥ 0.90 confirmed agreement as determined by neuromuscular physicians. In an assessment of 12 patients with LEMS, the CP was 0.92. Interrater reliability testing showed an average difference in 3TUG times measured did not exceed 20% for any of the pairs, resulting in a CP of 1.0 in all groups assessed.

The primary efficacy end point in DAPPER was the categorization of the degree of change in the 3TUG test (last observation at the theoretical peak drug effect, i.e., 2 hours post dose) upon withdrawal of active medication (stage II), when compared with time-matched average of the 3TUG assessments during stage I. In DAPPER this was categorized as > 30% deterioration in 3TUG time.

Subject Self-Assessment of LEMS-Related Weakness (W-SAS): The secondary efficacy end point in DAPPER was the W-SAS, a single item global self-assessment scale for LEMS-related weakness. The W-SAS was assessed at the end of stage II as compared to the baseline. The W-SAS assesses weakness using a 7-category scale with numerical values where weakness is ranked along a continuum from “Much much weaker” (–3) to “Much much stronger” (+3). No studies assessing validity, reliability, or minimally important difference (MID) of the W-SAS were identified for patients with LEMS.

Compound muscle action potential (CMAP): CMAP was assessed as another end point in DAPPER. CMAP measures the response of individual muscles to nerve stimulation. CMAPs were assessed at the trough before the first dose of the day and at the theoretical peak (2 hours after the first dose) using 1 nerve-muscle combination identified during the optimization procedure. CMAP optimization on the day of admission was used to determine the most responsive nerve-muscle combination. CMAP comparisons between stages were time specific. A decrease between time-matched CMAPs of stages I and II was considered confirmatory of deterioration in 3TUG.

Lower Extremity Function Scale (LEFS): The LEFS is a 20-item patient-reported outcome measure commonly used to assess mobility in patients with orthopedic conditions. The scale is 1 page and items are rated on a 5-point scale from 0 (extreme difficulty/unable to perform activity) to 4 (no difficulty). The total possible score is 80 and indicates a high functional level. Construct validity was established in a population with lower extremity musculoskeletal dysfunction by comparison with the SF-36 physical function subscale (r =.80), SF-36 physical component summary scores (r =.64), and the SF-36 mental component summary score (r =.30).[22] No MID for the LEFS was identified for patients with LEMS. A MID of 9 points has been identified for the population with lower extremity musculoskeletal dysfunction. The LEFS was an exploratory outcome in the DAPPER study.

Activities of Daily Living

LEMS-related ADLs were used as a functional measurement in DAPPER. LEMS-related ADLs were assessed as a 6-item patient-reported outcome measure. The outcomes were scored from 1 (worst) to 4 (best) and include toileting/bathing, dressing, eating/drinking, sit-to-stand, grooming, and bed-mobility. No studies assessing validity, reliability, or MID of LEMS-related activities of daily living were identified for patients with LEMS. LEMS-related ADLs were assessed as an exploratory outcome in the DAPPER study.

Efficacy

In DAPPER, the primary efficacy outcome assessment demonstrated that significantly more patients in the taper to placebo arm exhibited a deterioration of 30% or greater on the 3TUG test compared to the continuous amifampridine arm. None of the patients in the continuous amifampridine arm had a deterioration of 30% or greater in the final (blinded) 3TUG test after withdrawal of study drug (stage II), compared to 72.2% (n = 13) of patients in the taper to placebo arm (P < 0.0001). The treatment effect based on 3TUG was in favour of continuous amifampridine. According to clinical experts consulted by CADTH, the use of the 3TUG is considered to be a preferred component of assessing treatment response in patients with LEMS in clinic. The assessment of this outcome was based on a threshold of 30% or greater deterioration in 3TUG time, which is clinically relevant based on the literature and input from clinical experts consulted for the CADTH review.

The secondary efficacy end point in DAPPER, the W-SAS provided a global self-assessment that demonstrated an increase in weakness in the taper to placebo arm compared to the continuous amifampridine arm. The mean W-SAS final score was greater in the continuous amifampridine arm compared to the taper to placebo arm (–0.2; standard deviation [SD] = 1.19 versus –2.4 SD = 0.85; P < 0.0001, respectively). Inference for this secondary outcome is limited as it was not adjusted for multiple comparisons; this prevents firm conclusions from being drawn. No MID for patients with LEMS was identified in the literature; however the clinical experts consulted by CADTH determined that the results were clinically meaningful and similar to assessments of patients’ subjective response to treatment that are used in clinic.

Outcomes for CMAP, LEFS, and LEMS-related ADLs were reported descriptively without performing formal statistical testing. The mean (SD) CMAP assessment based on the change from baseline to the last available post-dose during stage II for all muscle types for patients treated with continuous amifampridine was –4.6% (28.95) and –48.5% (19.78) in the taper to placebo arm. The mean (SD) change from baseline in LEFS score was –2.6% (10.03) in the continuous amifampridine arm and –24.8% (16.43) in the taper to placebo arm. As a phase II trial, DAPPER was not designed to test multiple outcomes and did not have a statistical testing framework; therefore, firm conclusions cannot be made based on the assessments of outcomes for CMAP, LEFS, and LEMS-related ADLs. However, the clinical experts consulted by CADTH were of the view that the descriptive results of the CMAP, LEFS, and LEMS-related ADLs were clinically relevant and supported the primary and secondary efficacy outcomes.

LEMS-related symptoms, HRQoL, and outcomes related to productivity were also of importance to patients based on input received for this review. These outcomes were not assessed in DAPPER; thus, efficacy of amifampridine with respect to HRQoL and productivity remain unknown.

Harms (Safety)

In DAPPER, adverse events excluding LEMS-related signs and symptoms occurred in 5 patients (35.7%) in the continuous amifampridine arm and 12 patients (66.7%) in the taper to placebo arm. The most common adverse events were abdominal discomfort and respiratory tract infection, which each occurred in 2 patients (11.1%) in the taper to placebo arm.

In DAPPER, 1 patient (5.6%) in the taper to placebo arm experienced a serious adverse event of severe pneumonia.

The duration and design of DAPPER was limited and may not be a true reflection of the harms associated with amifampridine for all patients with LEMS. The patients included in DAPPER were not amifampridine-naive and were required to be on a stable and optimized dose of amifampridine and meet a threshold of responsiveness to amifampridine at baseline.

Cost and Cost-Effectiveness

Amifampridine is available as a 10 mg tablet, at a cost of $27.40 per tablet. The sponsor assumed the daily dosage of amifampridine was between 40 mg and 100 mg, depending upon severity of LEMS, corresponding to a cost of between $3,336 and $8,339 per patient per month, or between $40,027 and $100,067 per patient per year. Amifampridine is an add-on therapy to BSC, which the sponsor assumed to be comprised of some combination of pyridostigmine, immunosuppressants, intravenous immunoglobulin (IVIG) and/or plasma exchange, with the degree to which each of these is used (and the resulting cost of BSC) dependent upon disease severity, type of LEMS (non-tumour LEMS [NT-LEMS] or small cell lung cancer LEMS [SCLC-LEMS]) and whether BSC is provided alone or in combination with amifampridine. The maximum cost of BSC was assumed to be $1,329 per month, or $15,946 per year.

The sponsor submitted a cost-utility analysis of amifampridine in combination with 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 (NT-LEMS and SCLC-LEMS). 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, with a cycle length of 1 month. The 5 health states in the Markov model were based on categories of disease severity using QMG score: Asymptomatic (QMG score 0-1); Mild (QMG score 2-7); Moderate (QMG score 8-15); Severe (QMG score from 16-39); and Dead. Following treatment, patients could move to the next most severe health state, remain in the same health state, or move to the dead state. The effect of treatment on QMG score was derived from results published in a 2011 Cochrane review. The sponsor assumed that QMG scores would worsen by 10% annually for patients receiving BSC alone, with no worsening following treatment with amifampridine.

CADTH identified the following key limitations with the manufacturer's submitted economic analysis:

- CADTH's clinical review found that the QMG score is not considered to be 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 plus BSC on quality-adjusted survival and cost-effectiveness.

- The sponsor's assumption of LEMS worsening with BSC alone is not supported by clinical evidence. This results in all patients receiving BSC being in the worst possible health state within 5 years. This finding raises serious concerns about the model's face validity. This assumption was responsible for much (92%) of the estimated incremental effectiveness of amifampridine.
- The sponsor categorizes patients into severity-based categories. Health state utility was derived from the mean QMG score for each category. This model structure produces inappropriate assumptions about the relationship between small changes in QMG at the threshold of each category; that is, small QMG changes at the border between categories may have a disproportionate effect on QALYs.

CADTH was unable to conduct a reanalysis due to the identified issues with the sponsor's model and submitted evidence. Clinical experts and CADTH's clinical review agreed that the QMG is not an appropriate tool to measure LEMS severity, meaning that it is unlikely the predicted QALY gains neither reflect the true impact of amifampridine treatment nor capture what are meaningful aspects of LEMS for patients. A more robust estimate of treatment effectiveness would be particularly relevant given that the cost of amifampridine treatment is considerable (sponsor's estimate of lifetime incremental cost = $956,144 per patient). Collectively, these limitations severely limit the extent to which the sponsor's results can be interpreted. The sponsor's base-case estimate of the ICER was $453,809 per QALY; a price reduction of 71% was needed for amifampridine to be cost-effective at a WTP threshold of $50,000 per QALY. Due to the identified limitations, the cost-effectiveness of amifampridine is unknown and the necessary price reduction is likely much greater than the sponsor's base-case estimate.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Dr. Kerry Mansell, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

March 17, 2021 Meeting

Regrets

One expert committee member did not attend.

Conflicts of Interest

None

CADTH

Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

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.

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