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CADTH Reimbursement Recommendation

Cenobamate (Xcopri)

Indication: As adjunctive therapy in the management of partial onset seizures in adults with epilepsy who are not satisfactorily controlled with conventional therapy

Sponsor: Paladin Labs Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Xcopri?

CADTH recommends that Xcopri should be reimbursed by public drug plans as adjunctive therapy in the management of partial onset seizures in adults with epilepsy whose seizures are not satisfactorily controlled with conventional therapy, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Xcopri should only be reimbursed for the management of partial onset seizures in adults with epilepsy whose seizures are not satisfactorily controlled with conventional therapy, according to the criteria used by the public drug plans for other third generation antiseizure medication (ASMs) that are currently reimbursed for the management of partial onset seizures in adults with epilepsy whose seizures are not satisfactorily controlled with conventional therapy.

What Are the Conditions for Reimbursement?

Xcopri should only be reimbursed if the daily cost of Xcopri is the same as or lower than the daily cost of other third generation adjunctive therapies (lacosamide, brivaracetam, eslicarbazepine, and perampanel), and if the potential budget impact of funding Xcopri is addressed.

Why Did CADTH Make This Recommendation?

- Two clinical trials showed that Xcopri, when used concurrently with other ASMs, reduced the frequency of partial onset seizures compared with placebo.
- Xcopri may meet some needs that are important to patients with refractory partial onset seizures, such as reducing the occurrence of seizures.
- The CADTH Canadian Drug Expert Committee (CDEC) determined that there is not enough evidence to justify a greater cost for Xcopri compared with brivaracetam, eslicarbazepine, and perampanel.
- Based on public list prices, the sponsor estimated that reimbursement of Xcopri will lead to cost savings of approximately $1.7 million for the public drug plans over the next 3 years. However, the actual budget impact is uncertain, as CADTH identified several limitations that could not be reassessed given the sponsor's modelling approach.

Summary

Additional Information

What Is Epilepsy?

Epilepsy is a brain disorder that causes recurring seizures. Epilepsy may significantly interfere with patients' mental and physical health, daily activities, and life expectancy. It is estimated that 300,000 Canadians are living with epilepsy.

Unmet Needs in Epilepsy

Other treatment options are needed that eliminate or reduce seizures, have few adverse effects, and improve patients' quality of life.

How Much Does Xcopri Cost?

Treatment with Xcopri is expected to cost $3,214 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that cenobamate be reimbursed as adjunctive therapy in the management of partial onset seizures in adults with epilepsy whose seizures are not satisfactorily controlled with conventional therapy, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two double-blind (DB) randomized controlled trials (RCTs) (Study C013 [N = 222] and Study C017 [N = 437]), in adult patients with epilepsy whose partial onset seizures were not adequately controlled with up to 3 antiseizure medications (ASMs), demonstrated that 12 to 18 weeks of treatment with cenobamate resulted in a statistically significant and clinically relevant reduction in partial onset seizure frequency versus placebo. As adjunctive therapy, cenobamate 200 mg once daily showed a median 55.6% reduction in partial seizure frequency per 28 days compared with a 21.5% reduction in the placebo group of Study C013. In Study C017, the median percent reduction in seizure frequency per 28 days was 55.0%, 55.0%, and 24.0%, in the cenobamate 200 mg daily, 400 mg daily, and placebo groups, respectively.

Patients with partial onset seizures identified a need for treatments that decrease the frequency of partial onset seizures, as well as improve health-related quality of life (HRQoL). CDEC concluded that cenobamate may meet some of the needs identified by patients with refractory partial onset seizures including the reduction in seizure frequency. However, CDEC noted that the comparative benefit versus third generation ASMs lacosamide, brivaracetam, eslicarbazepine, and perampanel remains uncertain.

Using the sponsor-submitted price for cenobamate and publicly listed prices for all other drug costs, cenobamate dominated (i.e., was less costly and more effective than) brivaracetam, eslicarbazepine, and perampanel. As a result, cenobamate could be considered cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for adults with partial onset seizure epilepsy whose seizures are not satisfactorily controlled with conventional therapy and require adjunctive treatment. However, the estimated cost savings are sensitive to the baseline frequency of seizure (i.e., lower baseline frequency reduces estimated cost savings), which may have been overestimated in the sponsor's base case. Given the uncertainty around the comparative benefit, if cenobamate is considered similarly effective as brivaracetam, eslicarbazepine, and perampanel, the total drug cost of cenobamate should not exceed the total drug cost of brivaracetam, eslicarbazepine, or perampanel.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation, renewal, and prescribing		
1. Eligibility for reimbursement of cenobamate should be based on the criteria used by each of the public drug plans for initiation,	Two pivotal trials (Study C013 and Study C017), in patients with uncontrolled seizures despite treatment with 1 to 3 ASMs, demonstrated that cenobamate	—

Reimbursement condition	Reason	Implementation guidance
renewal, and prescribing of other third generation ASMs currently reimbursed for the management of partial onset seizures in adults with epilepsy whose seizures are not satisfactorily controlled with conventional therapy.	reduced the frequency of partial onset seizures relative to placebo. Direct evidence of the comparative efficacy of cenobamate vs. third generation ASMs was unavailable. There was uncertainty in the findings of the indirect evidence. Therefore, the potential benefit of cenobamate vs. other third generation ASMs currently reimbursed for management of partial onset seizures in adults with epilepsy whose seizures are not satisfactorily controlled with conventional therapy is not known.	
Pricing		
2. The daily cost of treatment with cenobamate should not exceed the daily cost of alternative third generation adjunctive therapies.	In the CADTH reanalysis, cenobamate was less costly and more effective than comparator treatments (i.e., cenobamate dominated brivaracetam, eslicarbazepine, and perampanel). However, both the cost savings and QALY gains were small relative to mean cost and quality-adjusted survival for all treatments. Given the high degree of uncertainty in the economic evidence, the price of cenobamate should be no greater than the negotiated price of the least costly comparator treatment.	—
Feasibility of adoption		
3. The feasibility of adoption of cenobamate must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	—

ASM = antiseizure medication; QALY = quality-adjusted life-year.

Discussion Points

- CDEC noted that there are numerous ASMs approved as adjunctive therapy for partial onset seizures, including 4 other third generation ASMs. There is no direct evidence to suggest that cenobamate offers a superior benefit over other adjunctive ASMs for partial onset seizures. The ITCs available suggest that patients receiving cenobamate may be more likely to experience a 50% or greater reduction in seizures in the short term than some other adjunctive ASMs. Several sources of heterogeneity were identified across the trials included in the ITCs, and it is uncertain whether the methods used to control for potential bias were adequate.

- Patients with refractory partial onset seizures identified a need for treatments that eliminate seizures with no or minimal adverse effects. Although the proportion of patients with a 100% reduction in seizure frequency versus baseline was reported in the studies, the potential benefit of cenobamate on seizure freedom remains unknown, primarily because the responder analyses were not included in the statistical testing hierarchy, and in Study C013, were conducted post hoc. In addition, the impact of cenobamate on HRQoL is unknown, as this outcome was only reported for 116 of 437 patients in Study C017, and no between-group statistical testing was performed.
- CDEC discussed the input from the clinical expert, who stated that a 50% or greater reduction in partial seizure frequency response threshold is not in keeping with clinical practice, as the goal of therapy is to eliminate all seizures with a motor component, loss of awareness, and/or features that are considered disabling.
- Longer-term safety and efficacy is uncertain, as the pivotal trials were 12 to 18 weeks in duration. Additional longer-term safety data from open-label extension (OLE) studies and a prospective open-label safety study did not reveal other safety issues. However, the short duration of the trials in the context of proposed lifelong treatment led to uncertainty regarding the long-term clinical safety and effectiveness of cenobamate.
- CDEC discussed that there is limited evidence for the combination of cenobamate with other third generation ASMs. In the pivotal trials, approximately 20% of patients received concomitant lacosamide, but use with brivaracetam, eslicarbazepine, and perampanel was not reported.
- The estimate of incremental cost-effectiveness was highly sensitive to assumptions about the baseline frequency of seizure. Feedback from clinical experts suggested that the base-case estimate of seizure frequency was higher than expected. When a lower value was used in the scenario analysis, incremental cost savings and QALYs gained decreased, suggesting that the true incremental cost-effectiveness ratio (ICER) is uncertain and may warrant additional price reduction to ensure cost-effectiveness.

Background

Epilepsy is a chronic neurologic disorder that affects the physical and mental health of patients, and significantly interferes with daily activity as well as life expectancy. The broad categories of epileptic seizures include: partial onset (also known as focal), generalized, combined generalized and focal, and unknown onset. The estimated prevalence of active epilepsy is 5.96 per 1,000 population (95% confidence interval [CI], 5.38 to 6.61 per 1,000) based on a meta-analysis of international studies. It is estimated that 300,000 Canadians are living with epilepsy.

ASMs are the most common treatment for seizures and although ASMs help to control or reduce seizures, they are not a cure for epilepsy. While the aim of the treatment with ASMs is to eliminate seizures with no adverse effects, this may not be possible for all patients, and approximately 20 to 40% of patients are at risk of having refractory epilepsy. Treatment options in patients with refractory epilepsy may be limited.

Cenobamate has been approved by Health Canada as adjunctive therapy in the management of partial onset seizures in adults with epilepsy who are not satisfactorily controlled with conventional therapy. Cenobamate is an ASM that is available as 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg oral tablets. The usual maintenance dose of cenobamate in the product monograph is 200 mg once daily. The maximum daily dose is 400 mg once daily, if needed, based on clinical response and tolerability.

Sources of Information Used by the Committee

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

- a review of 2 DB placebo-controlled RCTs in adults with uncontrolled partial seizures despite ongoing treatment with 1 to 3 ASMs
- patients' perspectives gathered by patient groups (the Canadian Epilepsy Alliance, Epilepsy Toronto, Epilepsy South Central Ontario, Epilepsy Southwestern Ontario, Epilepsy Association of Calgary, and Edmonton Epilepsy Association)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with epilepsy
- input from 1 clinician group, the Canadian League Against Epilepsy
- a review of the pharmacoeconomic model and report submitted by the sponsor
- indirect evidence from 2 network meta-analyses (NMAs)
- sponsor-submitted data from a prospective open-label safety study (Study C021), 2 OLE studies, and 3 additional studies to address gaps in the evidence.

Stakeholder Perspectives

Patient Input

Six patient groups — the Canadian Epilepsy Alliance, Epilepsy Toronto, Epilepsy South Central Ontario, Epilepsy Southwestern Ontario, Epilepsy Association of Calgary, and Edmonton Epilepsy Association — provided patient input for this review. The patient groups indicated that uncontrolled seizures and the adverse effects of ASMs affect patients' daily activities, independence (e.g., not being legally permitted to drive), and mental health (e.g., higher risks of depression, anxiety, and suicidal ideations). The patient groups noted that the whole family is also affected, and patients are often unemployed or underemployed and are also negatively affected by other social determinants of health. The patient groups noted that the most important treatment outcome is seizure freedom, with an alternative expectation of reduction in seizure frequency and/or severity of seizures. Patients and their families were also highly concerned about adverse effects of ASMs and the interactions between drugs. The patient groups indicated that new drugs would offer hope to patients who are close to giving up, and even a reduction in the absolute number of seizures can potentially improve overall quality of life.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

The expert stated that treatment options are limited for the approximately 30% of patients with focal epilepsy who do not respond to ASMs, and while ASMs may reduce seizure frequency, none offer a cure for epilepsy. Tolerability of ASMs can be an issue, and a patient's comorbidities and concomitant medications may contribute to the development of adverse effects. The clinical expert stated that cenobamate is best suited to patients with focal epilepsy who have not responded to conventional ASMs, and they anticipate it will be used as second-line or third-line therapy, typically as add-on therapy. Treatment response would be demonstrated by a reduction in seizure frequency or achieving seizure freedom, improvement in quality of life, and acceptable tolerability. According to the clinical expert, patients prescribed cenobamate should be under the care of a neurologist or epileptologist, in either a community or hospital setting.

Clinician Group Input

One clinician group provided input for this review: the Canadian League Against Epilepsy, which has more than 125 health care–related members. The group highlighted that there is an unmet need for more effective treatments for patients with uncontrolled, focal onset seizures. Despite the availability of several ASMs, there has been no meaningful improvement in epilepsy treatment–related outcomes and no significant increase in seizure freedom rates in the past 20 years. The clinician group noted that cenobamate would likely be used in combination with other available treatments (as an add-on) and is unlikely be used as a monotherapy. However, if cenobamate proves to prevent seizures once added, occasionally physicians will try to minimize a patient's ongoing treatment and may wean off other ASMs. There was consistency between the clinical expert consulted by CADTH and the Canadian League Against Epilepsy with regard to how response to treatment is assessed; reasons for discontinuing therapy; treatment setting; and specialists required to diagnose, treat, and monitor patients who may receive cenobamate.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH Reimbursement Review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for cenobamate:

- relevant comparators
- considerations for initiation of therapy
- considerations for prescribing of therapy.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Brivaracetam, eslicarbazepine, perampanel, and lacosamide are all listed as restricted benefits with specified criteria in most FPT drug plans. Is cenobamate expected to cause a shift in the current treatment paradigm? Would cenobamate be added to other third generation ASMs (e.g., brivaracetam, eslicarbazepine, perampanel, or lacosamide)?	The clinical expert noted to CDEC that it is not expected that cenobamate would cause a shift in the current treatment paradigm and stated it would be reasonable to reimburse cenobamate using similar criteria to the other third generation drugs. CDEC agreed with the clinical expert that cenobamate could be used in combination with other third generation ASMs.
Considerations for initiation of therapy	
Should initiation criteria of cenobamate be aligned with that of third generation ASMs?	CDEC and the clinical expert agreed that the initiation criteria for cenobamate should be aligned with the criteria used by each of the public drug plans for initiation of other third generation ASMs currently reimbursed for the management of partial onset seizures in adults with epilepsy who are not satisfactorily controlled with conventional therapy. CDEC and the clinical expert agreed that first generation ASMs (such as ethosuximide, carbamazepine, and valproate) and second generation ASMs (such as lamotrigine, clobazam, topiramate, oxcarbazepine, and levetiracetam) are considered conventional therapies for the management of partial onset seizures.
Considerations for prescribing of therapy	
Should prescribing criteria of cenobamate be aligned with that of third generation ASMs?	CDEC and the clinical expert agreed that the prescribing criteria for cenobamate should be aligned with the prescribing criteria used by each of the public drug plans for other third generation ASMs currently reimbursed for the management of partial onset seizures in adults with epilepsy whose seizures are not satisfactorily controlled with conventional therapy.

ASM = antiseizure medication; CDEC = CADTH Canadian Drug Expert Committee; FPT = federal, provincial, and territorial.

Clinical Evidence

Pivotal Studies and RCT Evidence

Description of Studies

The pivotal and RCT evidence included 2 DB placebo-controlled RCTs of add-on therapy with cenobamate in adults with uncontrolled partial seizures despite ongoing treatment with 1 to 3 ASMs. In Study C013, 222 patients were randomized to cenobamate 200 mg daily or placebo, and in Study C017, 437 patients were randomized to cenobamate 100 mg, 200 mg, or 400 mg once daily, or placebo, in addition to the ASMs initiated before enrolment. The studies included an 8-week baseline period before randomization, a 6-week dose titration period, plus a 6-week (Study C013) or 12-week (Study C017) maintenance period during which the dose of study drug remained stable. The primary end point was the percent change in

seizure frequency per 28 days versus baseline for all simple partial motor, complex partial, and secondarily generalized seizures. The key secondary outcome was the proportion of patients who experienced at least a 50% reduction in partial seizure frequency versus baseline. In both studies, these end points were calculated based on the entire DB treatment period (titration and maintenance phases) and used to support regulatory approval in the US. Study C017 conducted alternate analyses based on seizure data from the maintenance phase only, which were used to support regulatory approval in Europe.

The mean age of patients enrolled in the pivotal trials ranged from 36.2 years (standard deviation [SD] = 11.3) to 40.9 years (SD = 12.4) across treatment groups. There was roughly an equal proportion of males (47% to 54%) and females (46% to 53%) enrolled. In Study C013, the median baseline seizure frequency per 28 days was 5.5 (range, 2 to 237) in the placebo group and 7.5 (range, 0 to 187) in the cenobamate 200 mg group. In Study C017, the median baseline seizure frequency per 28 days was 8.4 (range, 4 to 704) in the placebo group and 11.0 (range, 4 to 418) in the cenobamate 200 mg group. On average, the enrolled patients had been diagnosed with epilepsy more than 20 years earlier, and patients in Study C017 had previously been treated with a median of 3 prior ASMs (range, 1 to 9).

The CADTH review focused on data for the cenobamate 200 mg to 400 mg dosage range, as per the draft product monograph.

Efficacy Results

For the primary end point in Study C013, the cenobamate 200 mg group showed a median 55.6% reduction in partial seizure frequency per 28 days, compared with a 21.5% reduction in the placebo group ($P < 0.0001$). In Study C017, the median percent reduction in seizure frequency per 28 days was 55.0%, 55.0%, and 24.0% in the cenobamate 200 mg, 400 mg, and placebo groups, respectively ($P < 0.001$), favouring cenobamate versus placebo for both dosage groups.

For the responder analysis in Study C013, 50.4% of patients in the cenobamate 200 mg group and 22.2% of patients in the placebo group experienced at least a 50% reduction in seizure frequency during the DB treatment period (odds ratio [OR] = 3.94; 95% CI, 2.14 to 7.24; $P < 0.0001$; not controlled for type I error rate). In Study C017, 57.8%, 60.4%, and 21.7% of patients in the cenobamate 200 mg, 400 mg, and placebo groups, respectively, experienced at least a 50% reduction in seizure frequency per 28 days during the DB treatment phase. The analyses favoured the cenobamate groups versus placebo (both $P < 0.001$, not controlled for type I error rate). The alternate analyses, which were based on the treatment response in the maintenance period only, reported 56.1%, 64.2%, and 25.5% of patients experienced at least a 50% reduction in seizure frequency per 28 days in the cenobamate 200 mg, 400 mg, and placebo groups, respectively. For this alternate primary end point, the differences favoured the cenobamate 200 mg ($P < 0.001$) and 400 mg groups ($P < 0.001$) versus placebo.

The proportion of patients who experienced at least a 75%, 90%, and 100% reduction in seizure frequency during the DB period and the maintenance period favoured the cenobamate 200 mg and 400 mg groups versus placebo; however, there was no control of type I error rate for these analyses in either study, and in Study C013, these analyses were conducted post hoc. While these results are generally supportive of the

efficacy of cenobamate, the data should be interpreted in light of the potential inflated risk of type I error and risk of bias associated with post hoc analyses.

Of note, Study C017 also included a 100 mg cenobamate dosage group, which is half the Health Canada–recommended maintenance dose. The percent reduction in seizure frequency per 28 days and the proportion of patients who experienced at least a 50% reduction in seizure frequency both favoured the cenobamate 100 mg group versus placebo, but other secondary outcomes, such as the higher responder thresholds, failed to detect a difference between groups.

HRQoL was not assessed in Study C013, and only descriptive data were available in Study C017 for approximately one-quarter of the patients enrolled. No meaningful change in HRQoL was observed in Study C017, based on data from the Quality of Life in Epilepsy Questionnaire (QOLIE-31-P).

Other outcomes of interest to patients, such as functional status, were not assessed, nor were seizure-free days or treatment retention, which were outcomes specified in the sponsor's protocol.

Harms Results

During the 12-week to 18-week treatment periods, adverse events were reported by 65%, 76%, and 90% of patients who received cenobamate 100 mg, 200 mg, and 400 mg, respectively, compared with 63% to 70% of patients who received placebo in Study C013 and Study C017. The most frequently reported adverse events in the cenobamate groups were somnolence (19% to 37%), dizziness (18% to 33%), fatigue (11% to 24%), and diplopia (4% to 15%). In the placebo groups, somnolence was reported in 8% to 12% of patients, dizziness in 14% to 17%, fatigue in 6% to 8%, and diplopia in 2% to 3% of patients.

In Study C013, 5 patients (4%) in the cenobamate group and 3 patients (3%) in the placebo group stopped treatment due to adverse events, whereas in Study C017, 11 patients (10%), 15 patients (14%), 22 patients (20%), and 5 patients (5%) stopped treatment due to adverse events in the cenobamate 100 mg, 200 mg, 400 mg, and placebo groups, respectively.

No deaths occurred during the pivotal trials. Serious adverse events were reported in 3% to 9% of patients who received cenobamate, and 4% to 6% who received placebo. One patient in the cenobamate 200 mg group in Study C017 developed a drug reaction with eosinophilia and systemic symptoms (DRESS) on day 24 that the investigator considered probably related to the study drug, and the study drug was stopped. Other dermatologic reactions that led to study drug withdrawal were reported in 2 patients in the cenobamate 200 mg group. In Study C013, 1 patient who was randomized to cenobamate experienced a serious drug hypersensitivity reaction on day 1. The patient stopped cenobamate treatment and recovered after 22 days. Suicidal ideation was reported by 1 patient in each treatment group in Study C013, and in 2 patients in the cenobamate 100 mg and 1 patient in the cenobamate 200 mg group in Study C017. One patient in the cenobamate 100 mg group in Study C017 attempted suicide.

Critical Appraisal

The risks of bias related to randomization, treatment allocation, and blinding in the pivotal trials were rated as low by the CADTH reviewer. At baseline, the patient characteristics appeared to be reasonably well

balanced between groups within the studies. In Study C013, the proportion of patients who discontinued was similar in both groups (10% and 9%), but Study C017 showed differential losses to follow-up, with 12%, 18%, 27%, and 13% of patients stopping treatment in the cenobamate 100 mg, 200 mg, 400 mg, and placebo groups, respectively. As a result, it is not clear if the treatment groups remained balanced throughout the study. Both trials measured the change in partial seizure frequency as well as the proportion of responders (≥ 50%) as primary and secondary end points. The analyses included all simple partial motor, complex partial, and secondarily generalized seizures, which the clinical expert agreed was appropriate for this population. While the 50% response threshold has been used in other ASM clinical trials and may be accepted as a minimal clinically important difference, the clinical expert indicated that higher response thresholds are desired, and the goal of therapy is seizure freedom. Other seizure response thresholds were tested in both studies, but these analyses were not controlled for type I error rate, and in Study C013 were conducted post hoc. Moreover, the responder analyses were conducted using last observation carried forward for Study C013, and with no imputation for missing data in Study C017; thus, patients who withdrew early could be considered treatment responders. Considering that patients who discontinue are likely to have worse outcomes than those who continue, it is possible the results of Study C017 may be biased in favour of cenobamate, due to the extent of the early withdrawals and the differential losses. However, the magnitude of any potential bias and the impact on the overall findings is unclear.

Neither of the pivotal trials was designed to test the impact of cenobamate on HRQoL or patients' ability to work or maintain independence. Although Study C017 collected data using the QOLIE-31-P instrument, this information was only gathered from approximately 25% of the patients enrolled and was reported descriptively. Moreover, the trials lacked an active comparator group and were 12 weeks to 18 weeks in duration, and thus can only address short-term efficacy and safety versus placebo. The sample size and duration of the studies were insufficient to capture rare adverse events.

No major issues were identified by the clinical expert on the generalizability of the pivotal studies, although it should be noted that both studies had extensive exclusion criteria and were limited to adults aged younger than 70 years. The trials used a more rapid titration schedule than has been recommended in the product monograph, which may affect the occurrence of some adverse events.

Long-Term Extension Studies

Description of Studies

Additional longer-term safety data were available from 2 single-arm OLE studies: Study C013 OLE and Study C017 OLE. Patients who completed the randomized phase of Study C013 were eligible to enter the Study C013 OLE phase (N = 149) and received open-label cenobamate at a daily maximum dose of 400 mg daily for up to 8.6 years. Only safety outcomes were assessed in Study C013 OLE. Patients who completed Study C017 were eligible to enter the Study C017 OLE phase (N = 356) and were transitioned to open-label cenobamate at a target dose of 300 mg once daily, in which efficacy outcomes of seizure control up to 48 months, and safety outcomes up to 6.4 years, were assessed.

Efficacy Results

For Study C017 OLE, Klein et al. (2022) reported interim efficacy outcomes based on a median exposure duration of 53.9 months (range, 1.1 months to 68.7 months), with retention rates at 12 months, 24 months, 36 months, and 48 months of 83%, 71%, 65%, and 62%, respectively. Among patients who remained on cenobamate, the treatment effects appear to be maintained up to 48 months. The median 65.4% reduction in partial seizure frequency versus baseline was reported during the first 6 months of the OLE (interquartile range [IQR], 52.0%; N = 354), with a 76.1% reduction (IQR, 44.8%) for months 43 to 48 (N = 213). Of the 354 patients who entered the OLE, 10.2% experienced 100% reduction in partial seizure frequency in the 36-month to 48-month month interval.

Harms Results

In both OLE studies, 89% of patients reported 1 or more treatment-emergent adverse events (TEAEs), of which dizziness (34% to 36%), somnolence (22% to 24%), and headache (17% to 28%) were the most common. Overall, 9% of patients stopped treatment due to adverse events and 22% to 26% of patients experienced a serious adverse event. There were no cases of DRESS or any serious skin and subcutaneous tissue disorders reported during the OLEs. Four deaths (3%) were reported in Study C013 OLE due to sudden unexpected death in epilepsy (SUDEP), cardiac arrest, respiratory arrest, and completed suicide. In Study C017 OLE, 6 patients (2%) died after experiencing myocardial infarction, cardiogenic shock, SUDEP, completed suicide, or sepsis.

Critical Appraisal

Limitations of the OLE studies include selection bias, lack of a control group, and lack of blinding. Since completion of a pivotal trial was an eligibility criterion for the extension study, patients who discontinued those trials due to adverse events or lack of response were excluded. This could result in a population of patients that was more tolerant of cenobamate, which can lead to: a response bias, as those not responding to treatment are less likely to continue; and biased estimates related to adverse events, potentially resulting in fewer and less serious adverse events being reported. Without comparator groups, the interpretation of the results in relation to an appropriate comparator (e.g., another ASM) is limited. Unblinding of the cenobamate treatment in the OLE can bias the reporting of end points, particularly for any subjective measures, including adverse events.

The sample sizes in Study C013 OLE (N = 149, with 25% completing the study) and Study C017 OLE (N = 356, with 20% completing the study) may not be sufficient to detect rare adverse events, and there was wide variance in follow-up duration for individuals. More common forms of morbidity (e.g., cardiac dysrhythmias) may not be easily identified as being related to drug exposure versus “natural” events unrelated to the drug.

Indirect Comparisons

Description of ITCs

Two indirect treatment comparisons (ITCs) were summarized and critically appraised for CADTH’s review of cenobamate. ITC1 was a sponsor-submitted NMA, which was designed to assess the relative efficacy and safety of adjunctive therapy with cenobamate compared to brivaracetam, perampanel, lacosamide,

eslicarbazepine acetate, and zonisamide in adult patients with partial onset seizures. ITC2 was a National Institute for Health and Care Excellence (NICE)–conducted NMA evaluating the relative efficacy and safety of ASMs used as add-on treatment for treating patients with partial onset seizures. Relevant treatments in ITC2 included brivaracetam, carbamazepine, cenobamate, eslicarbazepine acetate, gabapentin, ganaxolone, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenytoin, pregabalin, primidone, retigabine, rufinamide, sodium valproate, topiramate, vigabatrin, and zonisamide.

Efficacy Results

The sponsor-submitted NMA (ITC1) included 22 studies for the combined efficacy outcome of 50% or greater responder rate and seizure freedom. The results suggest that patients receiving cenobamate may be more likely to achieve a 50% or greater reduction in seizures or seizure freedom in the short-term, compared to any of the 5 ASMs in the NMA.

The ITC by NICE (ICT2) included 99 studies for the greater than 50% reduction in seizure frequency analysis, and 72 studies for the seizure freedom analysis. The results suggest that patients who received cenobamate may be more likely to achieve a greater than 50% reduction in seizure frequency in the short-term than most treatments, including eslicarbazepine acetate, retigabine, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, brivaracetam, pregabalin, rufinamide, zonisamide, and primidone. Relative treatment effects were not available for seizure freedom due to rarity of the event and insufficient statistical power.

Harms Results

The sponsor-submitted NMA included 20 studies for the safety outcome of TEAEs leading to treatment discontinuation. Compared to cenobamate, results for the 5 other ASMs had relatively wide 95% credible intervals (CrIs) that included the threshold of no difference, although this does not indicate equivalence between ASMs for this outcome. Due to the lack of precision in the estimates, firm conclusions cannot be made.

Harms data were reported numerically by treatment in ITC2, not comparatively, and did not inform relative safety for cenobamate versus other ASMs.

Critical Appraisal

The main limitations of both ITCs were the inclusion of non-adult patients (cenobamate is indicated for adults), missing relevant comparator ASMs (mainly in ITC1), and heterogeneity in patient and study characteristics across studies. Moreover, the limited reporting of trial data hindered the CADTH reviewers' ability to assess the consistency assumption, particularly for ITC2, and neither NMA conducted analyses to adjust for potential treatment effect modifiers. Differences across studies in how efficacy outcomes were defined (e.g., seizure freedom) and the treatment period they were based on (i.e., the entire treatment period or excluding the dose titration period) were assessed as important potential sources of bias. The duration of the trials was variable (7 weeks to 24 weeks) and limited to a short time frame for this chronic condition. Given these limitations, there was uncertainty in the results of the NMAs that prevented firm conclusions from being drawn from their findings. Furthermore, there was a lack of safety data and no information on

HRQoL or long-term outcomes reported in the ITCs; thus, it is not possible to estimate how cenobamate compares to other ASMs for these outcomes.

Studies Addressing Gaps in the Pivotal and RCT Evidence

Description of Studies

The sponsor submitted 1 prospective safety study (Study C021) and 3 additional studies to address gaps in the evidence.

Study C021 is a single-arm safety study of cenobamate as adjunctive therapy in patients with uncontrolled partial onset seizures despite treatment with 1 to 3 ASMs (N = 1,340). It consisted of a 12-month open-label treatment period, which included a 12-week titration phase followed by an open-label maintenance phase, with a target daily dose of 200 mg and a maximum daily dose of 400 mg.

The 3 additional studies submitted by the sponsor included: a study by Elizebath et al. (2021), which was a post hoc data analysis of HRQoL outcomes from all patients enrolled in Studies C013, C017, and C021 at a single US centre (N = 49); a study by Connor et al. (2022), which was a real-world evidence study among adults with a developmental disability (N = 28); and a study by Elliott et al. (2022), which was a real-world evidence study in patients with partial epilepsy who received cenobamate (N = 45, with 13 being adolescents aged between 12 years and 17 years).

Efficacy Results

Elizebath et al. (2021) reported that the mean overall QOLIE-31 (scale range, 1 to 100; a higher score indicates better quality of life) score measured for all patients who completed treatment was 67 (SD = 19; range, 32 to 97; n = 37) over a median treatment period of 5.6 years (range, 3 years to 8 years). Connor et al. (2022) reported that with adjunctive cenobamate treatment, mean focal seizures reduced from 20.9 seizures per month at baseline to 4.1 seizures per month at 6 months' follow-up (median from 3.0 seizures per month at baseline to 0.5 seizures per month at 6 months' follow-up); at 6 months, the responder rates greater than or equal to 50%, 75%, 90%, and 100% were 92.6%, 81.5%, 55.6%, and 48.2%, respectively. Elliott et al. (2022) reported that 60% of all included patients experienced at least a 50% reduction in seizures, and in the 13 adolescents, 8 (61.5%) experienced at least a 50% reduction in seizures. No efficacy results were reported in Study C021.

Harms Results

In Study C021, TEAEs occurred in 91% of patients, and the most frequently reported TEAEs were somnolence (31%), dizziness (29%), fatigue (19%), and headache (18%). Serious TEAEs occurred in 18% of the patients, and the most frequently reported serious TEAE was seizures (2%). A total of 183 patients (14%) had at least 1 TEAE leading to discontinuation, mostly frequently due to dizziness (1.4%) and seizures (0.8%). At the data cut off, 10 deaths had been reported in Study C021, with causes being laryngospasm, glioblastoma, subdural hematoma, SUDEP, sudden death, traumatic intracranial hemorrhage, hypovolemic shock, pneumonia viral, status epilepticus, and cardiac arrest. One case of sudden death was deemed by the investigator to be remotely related to study drug, and the rest were unrelated. No cases of DRESS were reported.

Connor et al. (2022) reported that adverse events occurred in 32% of the patients and included dizziness (14%), drowsiness (11%), ataxia (7%), and behavioural "acting out" (4%). Elliott et al. (2022) reported that the most frequently reported adverse event was somnolence (18%).

Critical Appraisal

Limitations of the other studies addressing the evidence gaps include the relatively small sample sizes for the observational studies, selection bias, lack of a control group, lack of blinding, and probable lack of control for confounding in the studies. Due to these factors, CADTH could not determine whether the results of these studies were valid or reliable.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults with partial onset epilepsy who are not satisfactorily controlled with conventional therapy (antiseizure medication) and require adjunctive therapy
Treatment	Cenobamate
Dose regimen	Loading dose: 12.5 mg daily for 14 days Titration: Each of 25 mg, 50 mg, 100 mg, and 150 mg daily for 14 days Maintenance: 200 mg once daily
Submitted price	Cenobamate, 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, 200 mg: $8.80 per tablet
Treatment cost	$3,214 (annual); $8.80 (daily)
Comparators	Brivaracetam Eslicarbazepine Perampanel Lacosamide[a]
Perspective	Canadian publicly-funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (100 years)
Key data sources	• Cenobamate trials: C017 (pivotal efficacy), C017 OLE, C013 (pivotal efficacy), C021 (phase III safety) • Sponsor-submitted NMA estimating relative treatment efficacy for 3 outcomes: seizure reduction, seizure freedom, and treatment discontinuation
Key limitations	• The relative clinical efficacy of cenobamate taken from the sponsor-submitted NMAs is uncertain. The CADTH clinical review concluded that the magnitude and clinical relevance of a seizure reduction is unclear, and no conclusions could be drawn on the relative effects of cenobamate on seizure freedom.

Component	Description
	• The model failed to incorporate treatment discontinuation due to nonresponse or a loss of response. Reliance on survival probabilities for treatment discontinuation alone resulted in implausible results, where patients continued treatment for years despite being considered nonresponders. • The predicted number of seizures was overestimated, which resulted in an overestimation of cenobamate's cost savings. This was due to an estimate of baseline seizure frequency that was not reflective of the patient population eligible for treatment with an adjunctive ASM. • The model failed to consider relevant comparators such as clobazam, topiramate, and levetiracetam. • The model failed to characterize the parameter uncertainty associated with the estimates of relative treatment effect obtained from the NMA. Additionally, parameter uncertainty for other inputs to the economic model were improperly characterized or not considered. • Estimates of relative treatment effect obtained from the NMA failed to capture all relevant sources of uncertainty. Considerable heterogeneity was observed regarding outcome definition, the time periods compared, and the duration of follow-up between trials. Each source of heterogeneity reflects additional imprecision that was not characterized in the economic evaluation.
CADTH reanalysis results	• The CADTH base case addressed some of the key limitations from the sponsor's submission. Changes were made to allow for discontinuation due to initial nonresponse or a subsequent loss of response, as well as the characterization of parameter uncertainty for the relative risk of a treatment response. • While the conclusions of the CADTH analyses were similar to those of the sponsor (that cenobamate is associated with higher QALYs and lower total costs than comparators), the magnitude of these findings was reduced. • There remains a high degree of uncertainty in the CADTH analyses, given the limitations with the comparative clinical efficacy of cenobamate and the absence of relevant comparators in the model. As such, it is unclear whether sufficient evidence exists to support a price premium for cenobamate over other relevant comparators.
Key scenario analyses	• CADTH conducted a scenario analysis to explore the impact of a lower baseline seizure frequency on the results of the economic evaluation. This led to a meaningful reduction in incremental costs. A more representative estimate of baseline seizure frequency would therefore reduce, and potentially eliminate, any potential cost savings from cenobamate.

ASM = antiseizure medication; LY = life-year; NMA = network meta-analysis; OLE = open-label extension; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified 5 key limitations in the sponsor's budget impact analysis (BIA). First, the use of a claims-based approach to estimate market size may have resulted in the misspecification of the budget impact of cenobamate. It was not clear what steps were taken to identify individual patients within the claims data. Second, the BIA failed to consider relevant comparators such as clobazam, topiramate, and levetiracetam. Third, estimates from the BIA were based on publicly available list prices for all comparators. The use of confidential negotiated prices for available comparators to cenobamate may lead to different conclusions about its budget impact. Fourth, market shares for lacosamide assumed it was used exclusively as an adjunctive therapy even though it is also indicated as a monotherapy. No steps were taken to identify the proportion of total lacosamide claims that were specific to adjunctive treatment. The estimated 3-year net budget impact was −$1,773,123 (Year 1: −$143,063; Year 2: −$602,201; Year 3: −$1,027,859).

CDEC Information

Members of the Committee

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

Meeting date: June 28, 2023

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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