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CADTH Reimbursement Recommendation

Cannabidiol (Epidiolex)

Indication: As adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older
Sponsor: Jazz Pharmaceuticals Canada, Inc.
Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Epidiolex?

CADTH recommends that Epidiolex be reimbursed by public drug plans as adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients aged 2 years and older, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Epidiolex should only be covered to treat patients aged 2 years or older who have a clinical diagnosis of seizures associated with LGS and experience at least 2 drop seizures per week over the course of 28 days, and whose seizures are not adequately controlled with 2 or more other antiseizure medications.

What Are the Conditions for Reimbursement?

Epidiolex should be reimbursed if prescribed by a physician with expertise in the diagnosis and management of patients with LGS and if the price of Epidiolex is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that treatment with Epidiolex, when added to background antiseizure medications, resulted in a reduction in drop seizure frequency over a 14-week treatment period and a higher proportion of patients reaching seizure control.
- Although Epidiolex does not impact the underlying condition in LGS, the evidence indicated that, as adjunctive therapy, it may meet the need for a new medication to achieve seizure control and reduce seizure burden for patients.
- Based on CADTH's assessment of the health economic evidence, Epidiolex does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Epidiolex is estimated to cost the public drug plans $29,429,895 over the next 3 years.

Additional Information

What Is LGS?

LGS is a rare and severe form of epilepsy that starts in childhood. Patients experience multiple types of seizures that cannot be completely controlled by medications and are associated with life-threatening injuries and

Summary

cognitive and behavioural impairments. The prevalence of LGS in Canada is estimated to be 12 in 100,000 people.

Unmet Needs in LGS

There is a need for new treatments to help patients attain and maintain seizure control with few side effects and better quality of life.

How Much Does LGS Cost?

Treatment with Epidiolex is expected to cost approximately $5,200 to $83,193 per patient per year, depending on patient weight and dosage.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that cannabidiol be reimbursed for the adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 2 randomized, placebo-controlled, phase III studies (the CARE 3 trial [N = 225] and CARE 4 trial [N = 171]) demonstrated that treatment with cannabidiol (at 10 mg/kg/day and 20 mg/kg/day doses), when added on to 1 or more (median = 3) background antiseizure medications (ASMs), may result in added clinical benefit for patients with LGS aged 2 to 55 years. In the CARE 3 trial, a statistically significant reduction was observed in median percentage change in drop seizure frequency after 14 weeks of treatment with cannabidiol 20 mg/kg/day (median difference −21.6%; 95% confidence interval [CI], −34.8 to −6.7; P = 0.0047) and cannabidiol 10 mg/kg/day (median difference −19.2%; 95% CI, −31.2 to −7.7; P = 0.0016), when compared to placebo. In the CARE 4 trial, a statistically significant reduction was observed in the median percentage change in drop seizure frequency after 14 weeks of treatment with cannabidiol 20 mg/kg/day (median difference −17.2%; 95% CI, −30.3 to −4.1; P = 0.0135), when compared to placebo. In addition, the results from the CARE 3 and CARE 4 trials showed that adjunctive cannabidiol (at both 10 mg/kg/day and 20 mg/kg/day doses) may be associated with a greater proportion of patients with at least a 50% reduction in drop seizures from baseline.

Patients identified a need for disease-modifying treatments that provide seizure control with sustained effectiveness, minimal adverse effects, and improved quality of life. Although there was insufficient evidence to evaluate the effects of cannabidiol on health-related quality of life (HRQoL) and drop seizure–free days, CDEC concluded that cannabidiol meets some patient needs by reducing seizure frequency and the associated burden for patients with LGS and their caregivers.

Using the sponsor-submitted price for cannabidiol and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for cannabidiol in combination with usual care was $186,373 per quality-adjusted life-year (QALY) compared with usual care alone. At this ICER, cannabidiol plus usual care is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for patients aged 2 years or older with LGS whose symptoms are inadequately controlled by usual care. A price reduction is required for cannabidiol to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with cannabidiol should be initiated in patients with seizures associated with LGS	Evidence from the CARE 3 and CARE 4 trials demonstrated that treatment with cannabidiol resulted in a reduction in median percentage	—

Reimbursement condition	Reason	Implementation guidance
who meet the following criteria: 1.1. aged 2 years or older 1.2. currently taking 1 or more ASMs at stable doses for at least 4 weeks before initiation.	change in drop seizure frequency in patients aged 2 to 55 years and currently receiving at least 1 ASM. The median number of concomitant ASMs received by the trial participants at the trial entry was 3.	
2. Patients must have the following: 2.1. at least 2 drop seizures per week over a 28-day period before initiation of cannabidiol 2.2. experienced treatment failure on at least 2 ASMs.	The CARE 3 and CARE 4 trials included patients who had at least 2 drop seizures each week during the 28 days of the baseline period. Patients in the CARE 3 and CARE 4 trials trial were required to have documented treatment failure on more than 1 ASM. CADTH reviewed no evidence to support the potential benefits and safety of treatment with cannabidiol in patients who did not meet the characteristics in this condition.	The Task Force of the ILAE Commission on Therapeutic Strategies proposed that drug-resistant epilepsy be defined as "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."[a]
Renewal		
3. The maximum duration of initial authorization is 6 months. For renewal after initial authorization, the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement.	The clinical experts noted that, in clinical practice, patients with LGS-associated seizures would ideally be seen every 3 to 6 months to monitor treatment response and perform any medication adjustments. As such, it is appropriate to require an assessment of response to treatment at least every 6 months.	—
Discontinuation		
4. Treatment with cannabidiol should be discontinued upon the occurrence of severe toxicity, lack of beneficial treatment effect, or intolerance.	This condition reflects the reasons for discontinuation in the CARE 3 and CARE 4 trials, supported by the input from clinical experts. CADTH did not review any evidence to demonstrate the safety and potential benefits of continuing cannabidiol in patients with this condition.	—
Prescribing		
5. Cannabidiol should be prescribed by a physician with expertise in the diagnosis and management of patients with LGS.	Accurate diagnosis and management of patients with LGS-associated seizures is important to ensure that cannabidiol is prescribed only for appropriate patients, and severe adverse effects are managed in an optimized and timely manner.	—
6. Cannabidiol should not be reimbursed in patients concurrently using cannabis products or other cannabinoid-based medications.	Recreation or medicinal cannabis or synthetic cannabinoid-based medications within 3 months before the trial entry or during the trial were prohibited in the CARE 3 and CARE 4 trials. CADTH did not review any evidence to demonstrate the safety or potential benefits of treatment with cannabidiol in patients listed in this condition.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
7. A reduction in price	The ICER for cannabidiol plus usual care is $186,373 when compared with usual care alone. A price reduction of 71% would be required for adjunctive cannabidiol to achieve an ICER of $50,000 per QALY compared to usual care alone.	—

ASM = antiseizure medication; ICER = incremental cost-effectiveness ratio; ILAE = International League Against Epilepsy; LGS = Lennox-Gastaut syndrome; QALY = quality-adjusted life-year.

[a]Kwan, P., et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069-77.

Discussion Points

- CDEC deliberated on evidence from 2 phase III, randomized, placebo-controlled studies (the CARE 3 and CARE 4 trials) evaluating the efficacy of cannabidiol in patients aged 2 to 55 years with a clinical diagnosis of LGS. In both trials, adjunctive treatment with cannabidiol was associated with statistically significant reductions in drop seizure frequency (primary end point) over a 14-week (2-week titration and 12-week maintenance) treatment period, when compared with placebo. The estimated differences in median percentage change from baseline between the cannabidiol 20 mg/kg/day and placebo groups were −21.6% (95% CI, −34.8 to −6.7; P = 0.0047) and −17.2% (95% CI, −30.3 to −4.1; P = 0.0135) in the CARE 3 and CARE 4 trials, respectively. The estimated difference in median percentage change from baseline between the cannabidiol 10 mg/kg/day and placebo groups was −19.2% (95% CI, −31.2 to −7.7; P = 0.0016). CDEC noted that although treatment with cannabidiol resulted in a statistically significant reduction in the median percentage change from baseline in drop seizure frequency (primary end point), no empirically derived minimally important difference (MID) was available to make a conclusion about the clinical meaningfulness of the observed difference in the primary study end point.
- CDEC noted that the CARE 3 and CARE 4 trials considered patients with at least a 50% reduction from baseline in the frequency of drop seizures during 28-day periods (key secondary end point) as treatment responders. The estimated differences between the cannabidiol 20 mg/kg/day and placebo groups were 25.0% (95% CI, 11.5% to 38.5%) and 20.7% (95% CI, 6.8% to 34.5%) in the CARE 3 and CARE 4 trials, respectively. The estimated difference between the cannabidiol 10 mg/kg/day and placebo groups was 21.1% (95% CI, 7.6% to 34.5%). The clinical experts considered a 20% to 30% between-group difference in the proportion of patients reporting at least a 50% reduction in drop seizures from baseline as a clinically meaningful difference. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of the evidence showed with moderate certainty that treatment with cannabidiol (at both 10 mg/kg/day and 20 mg/kg/day doses) may result in a greater proportion of patients reporting a reduction in drop seizures of 50% or more (key secondary end point) during the treatment period, compared to placebo.

- The CARE 3 and CARE 4 trials included patients who had at least 2 drop seizures per week during the 28 days before the trial entry (a minimum total of 8 drop seizures per 28 days). The patients enrolled in the pivotal trials experienced at least 10 drop seizures per 28 days, with a median number ranging across the study groups from 71.4 seizures (range, 10.3 to 855.9) in the cannabidiol 20 mg/kg/day group in the CARE 4 trial to 86.9 seizures (range, 14.0 to 7,494.0) for the placebo group in the CARE 3 trial. CDEC concluded that the benefit for patients with fewer than 8 LGS-associated seizures per 28 days remains unknown.
- CDEC discussed uncertainties in other outcome measures that were identified as important by patients and clinical experts, including seizure-free days and HRQoL. The clinical experts noted that nonmotor seizures can be difficult to detect, and therefore the frequency of motor-related seizures (i.e., drop seizures) is more objective for assessing antiseizure medication effects. In the CARE 3 and CARE 4 trials, the mean number of drop seizure–free days ranged from 2.7 days to 4.6 days in favour of treatment with cannabidiol versus placebo. However, this outcome was measured as an exploratory end point and was not included in the statistical testing hierarchy to control for type I error. CDEC also noted that the clinical significance of treatment effect on drop seizure–free days would be uncertain due to the lack of an MID. HRQoL was another important outcome identified by both patients and clinical experts. CDEC noted the treatment effect of cannabidiol on HRQoL was highly uncertain because of the risk of attrition bias, due to low questionnaire completion rates and missing outcome data for more than 50% of randomized patients in the CARE 3 and CARE 4 trials.
- Patients identified a need for disease-modifying treatments that provide seizure control with sustained effectiveness, minimal adverse effects, and improved quality of life. CDEC noted that cannabidiol did not meet the needs for correcting the underlying condition, achieving seizure freedom, or improving HRQoL, but may address the need for a new medication to achieve seizure control and reduce the burden of seizure for patients with this rare and life-threatening disease and their caregivers.
- CDEC discussed the feasibility of implementing a reimbursement recommendation for cannabidiol and considered the implementation issues raised by the drug programs. CDEC noted that there may be barriers to administration of cannabidiol due to the potentially challenging administrative steps involved with authorizing of medical cannabis, limited distribution options, and potential for drug wastage. CDEC also acknowledged that limited access to neurologists in some geographical regions may result in disparities for patients living in those areas. CDEC agreed with the clinical experts that availability of virtual consultation and follow-up with qualified neurologists could improve access.
- CDEC discussed the uncertainty in the economic analysis, specifically that in the absence of comparative evidence beyond 14 weeks, the incremental gain in QALYs with cannabidiol plus usual care predicted in CADTH's reanalysis may still overestimate the incremental benefits relative to usual care alone, and further price reductions may therefore be required.

Background

LGS is a lifelong, complex epilepsy syndrome associated with multiple seizure types that vary across patients. LGS presents in the first 4 years of life (peak age of onset: 3 to 5 years) in typically developing children, and is associated with refractory and multiple treatment-resistant seizure types, cognitive and behavioural impairments, and poor outcomes into adulthood. LGS has various etiologies, and patients exhibit multiple seizure types with distinctive electroencephalogram (EEG) features, including tonic seizures (stiffening of the body, upward eye gaze, dilated pupils, and altered breathing patterns) and atypical absence seizures (staring spells), followed by myoclonic jerks (sudden muscle jerks), tonic or atonic "drops" (brief loss of muscle tone), generalized tonic-clonic seizures (muscle stiffness and rhythmic jerking), and focal seizures. Atonic and tonic seizures can be accompanied by dangerous falls or "drop seizures" that often lead to injury. Indeed, LGS is considered a life-threatening condition associated with high rates of sudden unexpected death in epilepsy (SUDEP), and a risk of death among children with LGS that is 14 times higher than the risk in the US general population. Currently, LGS is diagnosed using clinical criteria; there are no specific diagnostic tests or biologic markers for the diagnosis of LGS. LGS affects between 3% and 10% of children with epilepsy, more commonly in males. The peak age for onset is between 3 and 5 years, with extreme incidence occurring in the first and 10th years of life. The prevalence of LGS in Canada, as estimated by the sponsor, is 12 in 100,000 people.

The goal of treatment is to achieve seizure freedom. In Canada, the only drugs currently indicated specifically for LGS are rufinamide and lamotrigine, both as add-ons to other ASMs. While lamotrigine is available through the Ontario Drug Benefit program, access to rufinamide must be obtained through the Exceptional Access Program. In addition to ASMs, most patients are also managed using enteral medications; dietary therapies such as ketogenic, modified Atkins, or low glycemic index diets; neuromodulation with vagus nerve stimulation or deep brain stimulation; and nonresective surgeries, such as corpus callosotomy. Surgical resection has limited use when the source of seizure activity can be identified. The clinical expert consulted by CADTH noted that purified cannabidiol from a licensed producer (so-called "artisanal cannabidiol" or medical cannabis) is available in Canada and has been used extensively for the treatment of drug-resistant LGS in children and adults, albeit at lower doses than what was used in clinical trials of cannabidiol.

Cannabidiol has been approved by Health Canada for the adjunctive treatment of seizures associated with LGS, Dravet syndrome, and tuberous sclerosis complex in patients aged 2 years and older. Cannabidiol is a cannabinoid. It is available as an oral solution, and the dosage recommended in the product monograph is up to a maximum dose of 10 mg/kg twice daily (20 mg/kg/day).

Sources of Information Used by the Committee

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

- a review of 2 double-blind, placebo-controlled, randomized, phase III clinical studies in patients aged 2 to 55 years with a clinical diagnosis of LGS-associated seizure

- a review of 1 single-arm, phase III, open-label extension study (the CARE 5 trial) in patients with a clinical diagnosis of LGS-associated seizure who had completed the pivotal studies (the CARE 3 and CARE 4 trials)
- patients' perspectives gathered by 1 patient group, the Canadian Epilepsy Alliance (CEA)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with LGS
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Patient group input was provided by the CEA. The CEA is a network of organizations supporting and advocating for people living with epilepsy and their families. Patient input was sourced from knowledge and experiences of patients, caregivers, clinicians, volunteers, donors, and funders, collected from 24 member associations. Based on input from the CEA, current treatments may fail in 30% of patients with epilepsy. According to the input, patients living with uncontrolled epilepsy are often socially isolated due to stigma and fear of rejection in social, work, and educational settings. Patients often experience depression and anxiety upon initial diagnosis, and continue to experience these conditions when ASMs stop working. Caregivers and family members are also impacted by epilepsy, as their lives may revolve around the seizures. Anxiety among caregivers is common, as they worry about when the next seizure will occur, the consequences of the epilepsy, and how to navigate social gatherings (e.g., when a young patient gets invited to a birthday party). In addition, caregivers often experience compassion fatigue because they cannot leave the patient alone, and are often sleep deprived due to sleep interruptions or anxiety, while living with many unpleasant side effects (e.g., mood swings, sexual dysfunction, suicidal thoughts, memory loss, fatigue, exhaustion, and so on) of the medications their loved ones are taking. Both patients and caregivers emphasized the importance of treatment that results in seizure freedom. However, patients and caregivers noted that they would accept a treatment that resulted in a reduction in the absolute number of seizures, as even a reduction in seizures could improve overall quality of life. Of note, because patients with intractable epilepsy are very often unemployed or underemployed, not covered under employer-funded insurance plans, and have restricted incomes, most drugs to treat their epilepsy are inaccessible. Accordingly, the CEA stressed the importance of having new medications placed on the provincial formulary so that patients with intractable epilepsy have access to novel treatments. Input provided by the CEA did not include input regarding experience with cannabidiol (Epidiolex).

Clinician Input

Input From Clinical Experts Consulted by CADTH

The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of LGS.

The clinical experts consulted by CADTH for the purpose of the review noted that despite the multiple treatment options available, there are currently no treatments available to reverse the course of LGS. Using the available treatment options, the overall prognosis of LGS remains unfavourable, and not all patients respond to the available treatment. The clinical experts added that there is a need for treatment that can meaningfully improve quality life for both patients and their caregivers. The clinical experts noted that despite its novel mechanism of action compared to available therapies, cannabidiol does not address the underlying disease process any more than other available treatments. Accordingly, the clinical experts suggest that cannabidiol would complement other available treatments as a symptom management treatment. The clinical experts opined that cannabidiol could be combined with 1 or 2 first-line antiseizure drugs. The clinical experts also felt that it would be reasonable to require adequate trials of 1 or 2 other ASMs before the use of cannabidiol. The clinical experts expected that the approval of cannabidiol would lead to a shift away from the use of medical cannabidiol in jurisdictions where cannabidiol is reimbursed by either public or private drug insurance plans. Based on input from the clinical experts, it is difficult to predict which patients with LGS would be most likely to benefit from cannabidiol. Patients whose symptoms have not responded to multiple ASMs are generally less likely to respond to the next ASM; however, these are the patients who are most in need of novel therapies. The clinical experts suggested that patients should be screened for treatment according to the clinician's judgment based on seizure characterization and frequency, etiology investigation, and previous ASM trialled, along with EEG interpretation. Based on the clinical experts' input, a clinically meaningful response to treatment in epilepsy is assessed as the median reduction in seizure frequency over a 28-day period, a 50% or greater seizure reduction, and seizure freedom rates (i.e., reduction of total seizures per day and seizure-free days per month). The clinical experts added that seizure frequency should be assessed every 4 weeks. The clinical experts also noted that quality of life for both patients and caregivers is an important secondary outcome. Based on the clinical experts' input, treatment with cannabidiol should be discontinued if patients develop persistent and progressive elevation of transaminases, and recurrent vomiting and diarrhea, which would compromise the absorption of antiseizure agents. In addition, treatment with cannabidiol should be reassessed if patients develop status epilepticus with no other reasonable explanation. Based on input received from the clinical experts, the prescribing and monitoring of cannabidiol for LGS should be limited to pediatric or adult neurologists who have special expertise in the management of epilepsy.

Clinician Group Input

No clinician group input was received with this submission.

Drug Program Input

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The 2 pivotal trials – the CARE 3 and CARE 4 trials – evaluated the efficacy and safety of cannabidiol and usual care versus usual care. From the comparator table, lamotrigine was missing. Lamotrigine	Comment from the drug programs to inform CDEC deliberations. The CADTH review team notes that lamotrigine is specifically indicated for LGS and is

Implementation issues	Response
is listed as 1 of 2 medications approved for seizure management in patients with LGS, with the other being rufinamide. Of note, the cost of lamotrigine is significantly less than the cost of rufinamide.	reimbursed by at least 1 Canadian jurisdiction, thereby meeting CADTH's criteria as a comparator. The current CADTH review of cannabidiol includes lamotrigine in the economic evaluation. Of note, in the CADTH review of rufinamide for LGS, lamotrigine was considered a relevant comparator.
Rufinamide is an ASM indicated for adjunctive treatment of seizures associated with LGS. CDEC recommends the following criteria for public drug coverage: • under the care of a physician experienced in treating LGS-associated seizures • currently receiving 2 or more antiepileptic drugs • in whom less costly antiepileptic drugs are ineffective or not approved. Health Canada is currently reviewing a generic submission for rufinamide. In the CARE 3 and CARE 4 trials, patients were required to have experienced treatment failure with more than 1 ASM. Patients were required to be stable on 1 or more ASMs. A task force of the International League Against Epilepsy recommended replacing the term "intractable" epilepsy with "drug-resistant" epilepsy and proposed that "drug-resistant" be defined as the failure of adequate trials of 2 tolerated, appropriately chosen and administered antiseizure medications (whether as monotherapy or in combination) to achieve seizure freedom.	Comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	
LGS diagnosis: • is based on signs and symptoms; genetic testing is not required • requires the presentation of a triad of the following characteristics: presence of multiple seizure types (i.e., tonic, atonic, and tonic-clonic); abnormal EEG patterns of slow-spike wave complexes; and moderate to severe cognitive impairment • in the CARE 3 and CARE 4 trials, required at least 8 drop seizures per 28-day period. Should all 3 of these characteristics be present to confirm a diagnosis of LGS? Should a minimum number of drop seizures per month be applied to diagnose LGS?	The clinical experts noted that the alignment of the diagnosis of LGS with the clinical presentations of the presence of multiple seizure types, abnormal EEG patterns of slow-spike wave complexes and paroxysmal fast activity, and moderate-to-severe cognitive impairment is reasonable. The clinical experts consulted by CADTH believed that the diagnosis of LGS should not be contingent on a minimum number of drop seizures per 28-day period. CDEC noted that the benefit of treatment with cannabidiol for patients with fewer than 8 LGS-associated seizures per 28 days remains unknown.
In the CARE 3 and CARE 4 trials, patients were required to have documented treatment failure with more than 1 ASM, and currently be stable on 1 or more ASM. To be eligible for cannabidiol, should patients be required to meet the definition of treatment-resistant epilepsy (failure of 2 or more ASMs), similar to rufinamide?	The clinical experts consulted by CADTH agreed that the definition of treatment-resistant epilepsy involves the failure of 2 or more ASMs, which aligns with the definition used in the CARE 3 and CARE 4 trials (i.e., treatment failure with more than 1 ASM). This is the also the threshold used to refer patients with LGS for epilepsy surgery. However, the threshold for defining treatment-resistant epilepsy may be set higher or lower depending on the circumstances. As noted by the clinical experts, some special conditions that prevent clinicians from prescribing traditional antiseizure

Implementation issues	Response
	medications, such as the presence of mitochondrial disorders or previous documented allergy to sodium channel blockers, should be carefully assessed for the possibility of prescribing cannabidiol in the setting of failure of 1 antiseizure drug.
Consider alignment with the reimbursement criteria for rufinamide, if appropriate.	Comment from the drug programs to inform CDEC deliberations.
Considerations for continuation or renewal of therapy	
What objective measures are used to assess and monitor therapeutic response in clinical practice?	Patient and/or caregiver feedback and clinical assessment are used to assess and monitor therapeutic response to treatment for seizures associated with LGS in the clinical practice setting. In some special circumstances, an EEG should also be considered as part of therapeutic response for patients with LGS, as per the clinician judgment.
In most jurisdictions, rufinamide receives indefinite coverage once approved. No renewal criteria were provided in the submission.	Comment from the drug programs to inform CDEC deliberations.
Considerations for discontinuation of therapy	
How would you define treatment failure?	The clinical experts indicated that the following events could be indictive of treatment failure in patients with LGS: • failure to control seizures or to reduce seizure frequency despite adequate dosing of current ASMs • poor tolerability to the therapy due to adverse reactions.
There are no discontinuation criteria identified in the CDR recommendations for rufinamide.	Comment from the drug programs to inform CDEC deliberations.
Considerations for prescribing of therapy	
The dosing schedule for cannabidiol as per the sponsor is: • initial dose 5 mg/kg/day for 1 week • maintenance dose 10 mg/kg/day up to a maximum of 20 mg/kg/day. How frequently do patients require the maximum recommended dose of 20 mg/kg/day?	The clinical experts stated that, in clinical practice, the maximum dose of any ASMs will always be attempted; however, many patients are unable to tolerate the maximum dose. As clinical experience with cannabidiol in patients with LGS is limited, the clinical experts were unable to comment how frequently the maximum dose of 20 mg/kg/day may be required or tolerated.
Cannabidiol is available as an amber liquid with 100 mg/mL of cannabidiol in a 100 mL bottle. Patients are titrated to effective therapeutic dose during the first 2 weeks of therapy. The patient or caregiver is required to measure the dose. Frequency of administration and volume of liquid (small quantities) has the potential to result in wastage.	Comment from the drug programs to inform CDEC deliberations.
There may be limited access to neurologists in some regions.	Comment from the drug programs to inform CDEC deliberations.
Patients were excluded from the CARE 3 and CARE 4 trials if they were taking more than 4 concurrent ASMs. As cannabidiol is intended to be used as adjunctive therapy, more information about drug interactions would be beneficial. Cannabidiol is a potent CYP3A4 and CYP2C19 inhibitor and is known to increase drug levels of clobazam, rufinamide, and topiramate.	Comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
Consider aligning prescribing criteria with rufinamide, if appropriate.	Comment from the drug programs to inform CDEC deliberations. The clinical experts consulted by CADTH for the purpose of this review agreed with this comment.
Generalizability	
Refractory epilepsy is a medical condition that is challenging to treat. Medical cannabis is used in this space. There will be interest in patients with refractory or drug-resistant epilepsy switching to a pharmaceutical-grade alternative for many reasons, including: • pharmacist involvement and medication review • barriers to access to medical cannabis, such as only being available by mail order or requirement of a credit card for purchase • physical labelling of product • coverage by public and/or private insurers[a] • consistent product availability • greater potency of cannabidiol compared to medical grade cannabis products, which typically have a maximum concentration of 50 mg/mL. In clinical practice, do you have challenges related to using the medical cannabis pathway supported by Health Canada? Do you foresee other patients with drug-resistant epilepsy pursuing access to cannabidiol?	The clinical experts noted that there are several challenges in navigating the medical cannabis pathway supported by Health Canada, including a lack of physician comfort with the paperwork involved with authorizing medical cannabis. The clinical experts believed it would be fair to assume that patients with other types of treatment-resistant epilepsy would pursue access to cannabidiol.
Care provision issues	
The indication population often presents with intellectual and physical disabilities. Communicating and reporting of side effects may be challenging in this population. Patients in the CARE 3 and CARE 4 trials were taking on average 3 ASMs concomitantly with cannabidiol, which can create uncertainty in the root cause of side effects.	Comment from the drug programs to inform CDEC deliberations.
System and economic issues	

The submitted list price for cannabidiol is $1,424.54 per 100 mL bottle. Cannabidiol is dosed according to weight; as such, there is a substantial cost increase with increased body weight and/or age. The price of cannabidiol by weight is as follows:
• **20 kg (44 lb)**
  ◦ 10 mg/kg/day = $28 per day
  ◦ 20 mg/kg/day = $56 per day
• **40 kg (88 lb)**
  ◦ 10 mg/kg/day = $56 per day
  ◦ 20 mg/kg/day = $112 per day
• **80 kg (176 lb)**
  ◦ 10 mg/kg/day = $112 per day
  ◦ 20 mg/kg/day = $224 per day
The price for the comparator drugs:
	Comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
• lamotrigine (adult) 400 mg/day is $6.60 per day or $2,409 annually • rufinamide[b] (adult maximum dose) 800 mg/day is $7.98 per day or $2,912 annually.	
Cannabidiol is an adjunctive therapy, and therefore the cost of other ASMs needs to be considered.	Comment from the drug programs to inform CDEC deliberations.
The cost of cannabidiol submitted by the sponsor is considerably higher than the medical cannabis (cannabidiol predominant) products. Patients who cannot afford upfront costs of this medication may resort to alternative pathways. Cannabidiol could have potential equity implications.	Comment from the drug programs to inform CDEC deliberations. The clinical experts consulted by CADTH for the purpose of this review agreed with this comment.

ASM = antiseizure medication; CDEC = Canadian Drug Expert Committee; ECG = electrocardiogram; LGS = Lennox-Gastaut syndrome; VAC = Veterans Affairs Canada.

[a]Currently only VAC and some private insurers cover medical cannabis products.

[b]Health Canada is currently reviewing a generic submission for rufinamide.

Clinical Evidence

Systematic Review

Description of Studies

Two studies were included in the sponsor-conducted systematic review: the CARE 3 and CARE 4 trials.

Both the CARE 3 and CARE 4 trials were multicentre, randomized, double-blind, phase III randomized controlled trials (RCTs) evaluating the efficacy of cannabidiol as adjunctive treatment in reducing drop seizures in patients aged 2 to 55 years with a clinical diagnosis of LGS.

In the CARE 3 trial, a total of 225 patients across 29 sites in 4 countries (US, Spain, France, and the UK) were randomized 1:1:1 to receive treatment with cannabidiol 20 mg/kg/day (n = 76), cannabidiol 10 mg/kg/day (n = 73), or volume-matched placebo (n = 76). Patients in the placebo group were split into 2 equivalent cohorts: half receiving 10 mg/kg/day (n = 38) dosing volumes, and half receiving 20 mg/kg/day (n = 38) dosing volumes. In the CARE 4 trial, a total of 171 patients across 24 sites in 3 countries (US, Netherlands, and Poland) were randomized to receive treatment with either cannabidiol 20 mg/kg/day (n = 86) or volume-matched placebo (n = 86). The randomization in both the CARE 3 trial and the CARE 4 trial was stratified by age group (2 to 5 years, 6 to 11 years, 12 to 17 years, and 18 to 55 years). Patients were titrated from a starting dose of 2.5 mg/kg up to 10 mg/kg/day over 7 days or 20 mg/kg/day over 11 days and remained at this dose level for the duration of the treatment period. Assigned treatments were add-ons to 1 or more background ASMs.

The primary efficacy end point for both trials was the reduction in the number of drop seizures (per 28 days) when compared with placebo in patients with LGS. Drop seizure was defined as a seizure event (atonic, tonic, or tonic-clonic) involving the entire body, trunk, or head that led or could have led to a fall, injury, slumping in a chair, or hitting the one's head on a surface. The key secondary outcome of interest was the number of patients considered treatment responders, defined as having a 50% reduction in drop seizures at the end

of the treatment period. Other outcomes that were assessed in the CARE 3 and CARE 4 trials included in the CADTH report included: proportions of patients who experienced a 25%, 75%, or 100% reduction in drop seizures at the end of the treatment period; number of inpatient hospitalizations due to epilepsy; and HRQoL as assessed by the Quality of Life in Childhood Epilepsy (QOLCE) questionnaire (for patients aged 2 to 18 years) or the Quality of Life in Epilepsy, Version 2 (QOLIE-31-P) questionnaire (for patients aged 19 years and older), and number of drop seizure–free days.

In the CARE 3 trial, the mean age of patients enrolled in the trial was 16.01 years (standard deviation [SD] = 10.77 years) in the cannabidiol 20 mg/kg/day group, 15.43 years (SD = 9.48 years) in the cannabidiol 10 mg/kg/day group, and 15.29 years (SD = 9.26 years) in the pooled placebo group. In the CARE 3 trial, the median number of drop seizures at baseline was higher in the cannabidiol 10 mg/kg/day group (median = 86.90; interquartile range [IQR], 14.0 to 7,494.0) than in the cannabidiol 20 mg/kg/day group (median = 85.53; IQR, 13.0 to 1,092.0) and the pooled placebo group (median = 80.25; IQR, 8.7 to 1,278.3). The proportion of patients reporting convulsive seizures lasting longer than 30 minutes was higher in the cannabidiol 20 mg/kg/day group (10.5%) than in the cannabidiol 10 mg/kg/day group (2.7%) and the pooled placebo group (3.9%). The mean number of prior ASMs was approximately 7, and the mean number of current ASMs being used at baseline was approximately 3 across treatment groups.

In the CARE 4 trial, the mean age of patients enrolled in the trial was 15.3 years (SD = 9.8 years) and 15.6 years (SD = 8.7 years) in the cannabidiol 20 mg/kg/day group and volume-matched placebo group, respectively. The median number of drop seizures at baseline was higher in the volume-matched placebo group (median = 74.67; IQR, 11.2 to 3,174.6) compared to the cannabidiol 20 mg/kg/day group (median = 71.43; IQR, 10.3 to 855.9). The mean number of ASMs was approximately 7, and the mean number of current ASMs being used at baseline was approximately 3 across treatment groups.

Efficacy Results

Percentage Change From Baseline in Drop Seizure Frequency

At the end of the 14-week treatment period in the CARE 3 trial, a reduction in median percentage change in drop seizure frequency was associated with treatment with cannabidiol 20 mg/kg/day (median difference = −21.6%; 95% CI, −34.8% to −6.7%; P = 0.0047) and cannabidiol 10 mg/kg/day (median difference = −19.2%; 95% CI, −31.2% to −7.7%; P = 0.0016), compared to the pooled placebo group.

At the end of the treatment period in the CARE 4 trial, a reduction in the median percentage change in drop seizure frequency was associated with treatment with cannabidiol 20 mg/kg/day compared to volume-matched placebo (median difference = −17.2%; 95% CI, −30.3% to −4.1%; P = 0.0135)

Reduction in Drop Seizures From Baseline of 50% or Greater

In the CARE 3 trial, during the treatment period, the difference in proportion of patients with at least a 50% reduction in drop seizure frequency from baseline between the cannabidiol 20 mg/kg/day group and the pooled placebo group was 25.0% (95% CI, 11.0% to 38.5%), and was 21.1% (95% CI, 7.6% to 34.7%) between the cannabidiol 10 mg/kg/day group and the pooled placebo group.

In the CARE 4 trial, the difference in proportion between the cannabidiol 20 mg/kg/day group and the volume-matched placebo group was 20.7% (95% CI, 6.8% to 34.5%).

Reduction in Drop Seizures From Baseline of 25% or Greater

In the CARE 3 trial, during the treatment period, the difference in the proportion of patients with at least a 25% reduction in drop seizure frequency from baseline between the cannabidiol 20 mg/kg/day group and the pooled placebo group was 18.4% (95% CI, 2.8% to 34.0%), and was 19.6% (95% CI, 3.9% to 35.3%) between the cannabidiol 10 mg/kg/day group and the pooled placebo group.

In the CARE 4 trial, the difference in proportion between the cannabidiol 20 mg/kg/day group and the volume-matched placebo group was 20.4% (95% CI, 5.8% to 35.1%).

Reduction in Drop Seizures From Baseline of 75% or Greater

In the CARE 3 trial, during the treatment period, the difference in the proportion of patients with at least a 75% reduction in drop seizure frequency from baseline between the cannabidiol 20 mg/kg/day group and the pooled placebo group was 22.4% (95% CI, 12.0% to 55.13%), and was 8.3% (95% CI, 0.3% to 16.3%) between the cannabidiol 10 mg/kg/day group and the pooled placebo group.

In the CARE 4 trial, the difference in proportion of patients with at least a 75% reduction in drop seizure frequency from baseline during the treatment period between the cannabidiol 20 mg/kg/day group and the volume-matched placebo group was 11.5% (95% CI, 1.3% to 21.8%).

Reduction in Drop Seizures From Baseline of 100%

No patients experienced a 100% reduction in drop seizure frequency during the treatment period in either the CARE 3 trial or the CARE 4 trial.

Number of Inpatient Hospitalizations Due to Epilepsy

In the CARE 3 trial, the number of patients with 1 or more inpatient hospitalizations due to epilepsy was 7 (9.2%) in the cannabidiol 20 mg/kg/day group, 6 (8.2%) in the cannabidiol 10 mg/kg/day group, and 6 (7.9%) in the pooled placebo group.

In the CARE 4 trial, the number of patients with 1 or more inpatient hospitalizations due to epilepsy was 10 (11.6%) in the cannabidiol 20 mg/kg/day group and 5 (5.9%) in the volumed-matched placebo group.

QOLCE for Patients Aged 2 to 18 Years

In the CARE 3 trial, overall QOLCE scores were available for 33 patients (43.4%) in the cannabidiol 20 mg/kg/day group, 36 patients (49.3%) in the cannabidiol 10 mg/kg/day group, and 38 patients (50%) in the pooled placebo group. At baseline, the overall mean QOLCE scores were comparable across the cannabidiol 20 mg/kg/day group, cannabidiol 10 mg/kg/day group, and the pooled placebo group, at 41.6 (SD = 15.6), 40.6 (SD = 15.4), and 41.4 (SD = 16.1), respectively. The adjusted mean treatment difference in change from baseline in overall QOLCE scores between the cannabidiol 20 mg/kg/day group and the pooled placebo group was −5.1 (−11.4 to 1.2), and was 1.6 (95% CI, −4.5 to 7.8) between the cannabidiol 10 mg/kg/day group and the pooled placebo group.

In the CARE 4 trial, overall QOLCE scores were available for 26 patients (30.2%) and 38 patients (44.7%) in the cannabidiol 20 mg/kg/day group and the volumed-matched placebo group, respectively. At baseline, the overall mean QOLCE scores were comparable between the cannabidiol 20 mg/kg/day group and the volume-matched placebo group at 39.5 (SD = 12.6) and 39.1 (SD = 15.2), respectively. The adjusted mean treatment difference in change from baseline in overall QOLCE scores between the cannabidiol 20 mg/kg/day group and the volume-matched placebo group was 3.7 (95% CI, −3.3 to 10.7).

QOLIE-31-P for Patients Aged 19 Years and Older

In the CARE 3 trial, total QOLIE-31-P scores were available for 13 patients in the cannabidiol 20 mg/kg/day group, 14 patients in the cannabidiol 10 mg/kg/day group, and 10 patients in the pooled placebo group. At baseline, the total mean QOLIE-31-P scores were 50.2 (SD = 16.6) in the cannabidiol 20 mg/kg/day group, 56.0 (SD = 19.2) in the cannabidiol 10 mg/kg/day group, and 62.5 (SD = 13.6) in the pooled placebo group. The adjusted mean treatment difference in change from baseline in total QOLIE-31-P scores between cannabidiol 20 mg/kg/day group and the pooled placebo group was 2.9 (95% CI, −0.3 to 13.1), and was 3.6 (95% CI, −7.0 to 14.3) between the cannabidiol 10 mg/kg/day group and the pooled placebo group.

In the CARE 4 trial, total QOLIE-31-P scores were available for 14 patients (16.3%) in the cannabidiol 20 mg/kg/day group and 14 patients (16.5%) in the volume-matched placebo group. At baseline, the total QOLIE-31-P scores were comparable between the cannabidiol 20 mg/kg/day group and the volume-matched placebo group, at 55.8 (SD = 13.5) and 57.3 (SD = 19.5), respectively. The adjusted mean treatment differences in total QOLIE-31-P were not calculated due to the low number of completed assessments.

Drop Seizure-Free Days

In the CARE 3 trial, the mean number of drop seizure–free days increased in all treatment groups at the end of the treatment period. Compared to the pooled placebo group, treatment with cannabidiol 20 mg/kg/day was associated with an increase in the mean number of drop seizure–free days of 4.6 days (95% CI, 2.5 to 6.8 days), while treatment with cannabidiol 10 mg/kg/day was associated with an increase of 3.3 days (95% CI, 1.2 to 5.5 days).

In the CARE 4 trial, the mean number of drop seizure–free days increased in both treatment groups at the end of the treatment period. Compared to the volume-matched placebo group, treatment with cannabidiol 20 mg/kg/day was associated with a mean increase of 2.7 days (95% CI, 0.7 to 4.7 days).

Other Outcomes

The following outcomes were noted as being meaningful by the patient group and clinical experts consulted by CADTH, but not assessed in either the CARE 3 or CARE 4 trials: SUDEP rate, employment, and HRQoL of caregivers.

Harms Results

Adverse Events

In the CARE 3 trial, at least 1 adverse event (AE) was reported among 93.9% of patients in the cannabidiol 20 mg/kg/day group, 83.6% of patients in the cannabidiol 10 mg/kg/day group, and 72.4% of patients in the pooled placebo groups.

In the CARE 4 trial, at least 1 AE was reported among 86.0% and 69.4% of patients in the cannabidiol 20 mg/kg/day group and volume-matched placebo group, respectively.

Serious Adverse Events

In the CARE 3 trial, at least 1 serious adverse event (SAE) was reported among 15.9% of patients in the cannabidiol 20 mg/kg/day group, 19.4% of patients in the cannabidiol 10 mg/kg/day group, and 10.5% of patients in the pooled 20 mg/kg/day and 10 mg/kg/day placebo groups.

In the CARE 4 trial, at least 1 SAE was reported among 23.3% and 4.7% of patients in the cannabidiol 20 mg/kg/day group and volume-matched placebo group, respectively.

Treatment Discontinuation Due to AEs

In the CARE 3 trial, discontinuation of treatment due to AEs was reported among 7.3% of patients in the cannabidiol 20 mg/kg/day group, 1.5% of patients in the cannabidiol 10 mg/kg/day group, and 1.3% of patients in the pooled placebo group.

In the CARE 4 trial, discontinuation of treatment due to AEs was reported in 14.0% and 1.2% of patients in the cannabidiol 20 mg/kg/day group and the volume-matched placebo group, respectively.

Mortality

There were no reported deaths in the CARE 3 trial. In the CARE 4 trial, 1 death (1.2% of patients) was recorded due to acute respiratory distress syndrome in the cannabidiol 20 mg/kg/day group.

Notable Harms

Notable harms of interest were related to nervous system disorders (i.e., somnolence, status epilepticus, and sedation), hepatocellular injury or investigation (i.e., increased alanine aminotransferase [ALT] and aspartate aminotransferase [AST], bilirubin elevation and serum transaminase elevation), and gastrointestinal disorders (i.e., diarrhea, vomiting, and constipation).

In the CARE 3 trial, somnolence, status epilepticus, and sedation were reported in 30.5%, 4.9%, and 3.7% of patients, respectively, in the cannabidiol 20 mg/kg/day group; in 20.9%, 10.4%, and 3.0% of patients, respectively, in the cannabidiol 10 mg/kg/day group; and in 5.3%, 3.9%, and 1.3% of patients, respectively, in the pooled placebo group. Increased levels of ALT, AST, and serum transaminase were reported in 4.9%, 3.7%, and 1.2% of patients, respectively, in the cannabidiol 20 mg/kg/day group; in 4.5%, 3.7%, and 1.5% of patients, respectively, in the cannabidiol 10 mg/kg/day group; and in 1.3%, 1.3%, and 0% of patients, respectively, in the pooled placebo group. The following investigations were not reported in the CARE 3 trial: abnormal liver function test, acute hepatic failure, and hepatotoxicity. Diarrhea, vomiting, and constipation were reported

in 14.6%, 12.2%, and 4.9% of patients, respectively, in the cannabidiol 20 mg/kg/day group; in 10.4%, 6.0%, and 4.5% of patients, respectively, in the cannabidiol 10 mg/kg/day group; and in 7.9%, 11.8%, and 3.9% of patients, respectively, in the pooled placebo group.

In the CARE 4 trial, somnolence, sedation, and status epilepticus were reported in 15.1%, 8.1%, and 1.2% of patients, respectively, in the cannabidiol 20 mg/kg/day group; and in 9.4%, 1.2%, and 1.2% of patients, respectively, in the volume-matched placebo group. The following hepatocellular injury and investigation AEs were reported in the cannabidiol 20 mg/kg/day group: increased ALT (9.3%), increased AST (7.0%), abnormal liver function test (4.7%), acute hepatic failure (3.5%), serum transaminase elevation (2.3%), hepatic failure (1.2%), and hepatotoxicity (1.2%). In the volume-matched placebo group, increased levels of ALT and AST were reported in 2.4% and 1.2% of patients, respectively. Diarrhea, vomiting, and constipation were reported in 18.6%, 10.5%, and 7.0% of patients, respectively, in the cannabidiol 20 mg/kg/day group; and in 8.2%, 16.5%, and 4.7% of patients, respectively, in the volume-matched placebo group.

Critical Appraisal

The CARE 3 and CARE 4 trials were multicentre, randomized, double-blind, phase III RCTs. In both trials, patients were randomized centrally using interactive voice response system (IVRS) technology, which is typically adequate for concealing allocation until treatment assignment. IVRS technology was also used to dispense the investigational product allowing the treatment concealment for both patients and the investigator to remain blinded. Although the CARE 3 trial included 4 treatment types (cannabidiol 20 mg/kg/day, cannabidiol 10 mg/kg/day, volume-matched placebo 20 mg/kg/day, and volume-matched placebo 10 mg/kg/day), the study participants were randomized using a 1:1:1 randomization ratio to the cannabidiol 20 mg/kg/day treatment group, cannabidiol 10 mg/kg/day treatment group, and the placebo treatment group. The placebo group was split in half for patients to receive either the 20 mg/kg/day placebo or the 10 mg/kg/day placebo, and study results were reported based on the pooled placebo group. While this approach is acceptable, it relies on the assumption that randomization was successful in each group. Differences in baseline characteristics between cannabidiol 20 mg/kg/day, cannabidiol 10 mg/kg/day, and the pooled placebo groups were noted in the following factors: the proportion of patients reporting convulsive seizures longer than 30 minutes, and concomitant use of benzodiazepine derivatives at baseline. According to the clinical experts consulted by CADTH for the purpose of this review, it is unknown if the previously mentioned imbalances could influence treatment response given the rarity of LGS. At CADTH's request, the sponsor reported that the assumptions related to splitting the placebo group and pooling results for analyses were not formally tested. However, the sponsor noted, as described in clinical study report for the CARE 3 trial, that post hoc sensitivity analyses were conducted on the primary outcome to determine if pooling the placebo group had an effect on the results. The analyses indicated that the efficacy response when cannabidiol 20 mg/kg/day was compared to placebo 20 mg/kg/day (and when the cannabidiol 10 mg/kg/day dose was compared to placebo 10 mg/kg/day) was similar to that for the doses versus the pooled placebo response. In the CARE 4 trial, the 1:1 randomization ratio and the randomization stratification factors appeared appropriate, and no notable baseline imbalances were observed between the cannabidiol 20 mg/kg/day group and the volume-matched placebo group.

In the CARE 3 trial, a higher proportion of patients in the cannabidiol 20 mg/kg/day group discontinued from the study compared to the cannabidiol 10 mg/kg/day and pooled placebo groups (approximately 12% versus approximately 3%). The higher discontinuation rate in the cannabidiol 20 mg/kg/day group appeared to be driven by AEs. In the CARE 4 trial, a higher proportion of patients in the cannabidiol 20 mg/kg/day group discontinued from the study compared to the volume-matched pooled placebo groups (9.3% versus 1.2%). The higher discontinuation rate in the cannabidiol 20 mg/kg/day group appeared to be driven by AEs. The application of the "missing not at random" assumption and sensitivity analysis exploring missing efficacy results due to treatment discontinuation suggests that bias due to uneven discontinuation was unlikely.

In both the CARE 3 and CARE 4 trials, all efficacy outcome measures were to be completed by the caregiver. To maintain consistency, the same caregiver, if patients had multiple caregivers, was to complete and answer the questionnaire and assessment. Seizure information in both studies was ascertained via patient or parent or caregiver report using an IVRS diary, while paper diaries were used to capture usage of the investigational product, concomitant medications, and AEs. Based on input from the clinical experts, patient and parent or caregiver reporting of seizures tended to be accurate for motor seizures; however, it was not very reliable or accurate for nonmotor seizures. Of note, seizure diaries are the standard method of collecting data for clinical trials, and the International League Against Epilepsy recommends the use of diaries for collecting seizure frequency data.[19] Both the CARE 3 trial and the CARE 4 trial assessed HRQoL — an outcome deemed important by both patients and clinicians — using validated and reliable instruments: the QOLCE and the QOLIE-31-P. The double-blind nature of the trials minimized risk of bias in the measurement of subjective items of the QOLCE and QOLIE-31-P. However, comparative efficacy conclusions based on the HRQoL outcomes are limited because the QOLCE and the QOLIE-31-P were not part of the hierarchical testing procedure, and also because of the low completion rate across treatment groups. Total QOLCE scores were available for 47.6% and 36.3% of patients in the CARE 3 and CARE 4 trials, respectively, while total QOLI-31-P scores were available for 16.5% and 16.4% of patients in the CARE 3 and CARE 4 trials, respectively. Consequently, assessment of HRQoL in both trials is at high risk of attrition bias, although the extent and direction of the bias cannot be determined because it is not clear if the patients who completed the questionnaires were systematically different from those who did not. Of note, as the completion rates were similar between the treatment groups within the CARE 3 and CARE 4 trials, there is little risk of bias that attrition favoured any 1 treatment group.

Analysis of efficacy results in the CARE 3 and CARE 4 trials followed a defined statistical analysis plan. The primary and key secondary outcomes were addressed using a hierarchical gatekeeping procedure, which controlled for type 1 errors. The sponsor conducted additional sensitivity analyses of the primary efficacy outcome using the per-protocol analysis set, and testing the assumption that data were not missing at random. In all scenarios, the sensitivity analyses were consistent with the primary efficacy analysis.

The clinical experts consulted by CADTH for the purpose of this review were unable to assess if the results of the CARE 3 and CARE 4 trials were applicable to patients in the Canadian clinical setting. However, the clinical experts did note trial details that were applicable to the Canadian clinical setting, and others that were not representative of clinical practice in Canada. Briefly, the clinical experts noted that the treatment periods in the CARE 3 and CARE 4 trials were long enough to detect a meaningful treatment response

on seizures in patients with LGS; however, it was uncertain if the treatment response observed could be sustained in the long term. Moreover, a longer study period would be required to detect a treatment response on cognitive functioning. In the Canadian setting, where the use of medicinal cannabis for adjunctive treatment of seizures associated with LGS can be accessed through the medical cannabis pathway supported by Health Canada, the clinical experts would not impose any sort of washout period before initiating pharmaceutical cannabidiol.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- change from baseline in number of drop seizures during the treatment period; proportion of patients considered treatment responders (defined as those with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in drop seizures from baseline); number of drop seizure–free days; and number of inpatient hospitalizations due to epilepsy
- quality of life, as measured by the QOLCE (for patients aged 2 to 18 years) or QOLIE-31-P (for patients aged 19 years and older)
- notable harms, including somnolence and sedation, hepatocellular injury, and gastrointestinal disorders.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of certainty of evidence assessment was the presence of a clinically important reduction in the frequency of drop seizures (i.e., percentage change in the drop seizure frequency) and proportion of patients considered treatment responders (i.e., proportion of patients with ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in drop seizures) on thresholds informed by clinical expert opinion. Other targets for the certainty of evidence were the presence or absence of a non-null effect for the number of drop-seizure days, number of inpatient hospitalizations due to epilepsy, and HRQoL as measured by the QOLCE or QOLIE-31-P.

Results of GRADE Assessments

Table 3 summarizes the detailed GRADE summary of findings for cannabidiol versus placebo in the pivotal CARE 3 and CARE 4 trials with patients aged 2 years and older with LGS. For the GRADE assessments, findings from the CARE 3 and CARE 4 trials were considered together and summarized narratively per outcome because these studies were similar in population, interventions, design, and outcome measures.

Table 3: Summary of Findings for Cannabidiol 10 mg/kg/day and Cannabidiol 20 mg/kg/day Versus Volume-Matched Placebo for Patients With Seizures Associated With LGS

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Reduction in drop seizure frequency				
Median percentage change from baseline in drop seizure frequency during the treatment period per 28-day cycle (95% CI) Follow-up: 14 weeks	396 (2 RCTs)	**CARE 3 trial** • Placebo: −17.2% (−37.1% to 0.9%) • Cannabidiol: 10 mg/kg/day: −37.2% (−63.8% to −5.8%) • Difference: −19.2% (−31.2% to −7.7%) • Cannabidiol: 20 mg/kg/day: −41.9% (−72.4% to −1.3%) ◦ Difference: −21% (−34.8% to −6.7%) **CARE 4 trial** • Placebo: −21.8% (−45.7% to 1.7%) • Cannabidiol 20 mg/kg/day: −43.9% (95% CI, −69.6% to −1.9%) ◦ Difference: −17.2% (−30.3% to −4.1%)	Moderate[a]	Cannabidiol 10 mg/kg/day and cannabidiol 20 mg/kg/day may result in little to no clinically important reduction in the median percentage change from baseline for frequency of drop seizures during the treatment period when compared to placebo.
Proportion of patients with ≥ 50% reduction in drop seizures from baseline during the treatment period (95% CI) Follow-up: 14 weeks	396 (2 RCTs)	**CARE 3 trial** • Placebo: 14.5% • Cannabidiol: 10 mg/kg/day: 35.6% ◦ Difference: 21.1% (7.6% to 34.5%) • Cannabidiol: 20 mg/kg/day: 39.5% ◦ Difference: 25.0% (11.5% to 38.5%) **CARE 4 trial** • Placebo: 23.5% • Cannabidiol 20 mg/kg/day: 44.2% ◦ Difference: 20.7% (6.8% to 34.5%)	Moderate[b]	Cannabidiol 10 mg/kg/day and cannabidiol 20 mg/kg/day may result in a greater proportion of patients reporting a reduction in drop seizures of 50% or more during the treatment period compared to placebo.
Proportion of patients with ≥ 25% reduction in drop seizures from baseline during	396 (2 RCTs)	**CARE 3 trial** • Placebo: 43.4% • Cannabidiol: 10 mg/kg/day: 63.0%	Moderate[d]	Cannabidiol 20 mg/kg/day may result in a greater proportion of patients reporting a reduction in drop seizures of 25% or more

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
the treatment period (95% CI)[c] Follow-up: 14 weeks		◦ Difference: 19.6% (3.9% to 35.3%) • Cannabidiol: 20 mg/kg/day: 61.8% ◦ O Difference: 18.4% (2.8% to 34.0%) • Cannabidiol: 10 mg/kg/day: 63.0% ◦ Difference: 19.6% (3.9% to 35.3%) **CARE 4 trial** • Placebo: 43.5% • Cannabidiol 20 mg/kg/day: 64.0% ◦ Difference: 20.4% (5.8% to 35.1%)		during the treatment period compared to placebo. Cannabidiol 10 mg/kg/day may result in little to no increase in the proportion of patients reporting a reduction in drop seizures of 25% or more during the treatment period compared to placebo.
Proportion of patients with ≥ 75% reduction in drop seizures from baseline during the treatment period (95% CI)[c] Follow-up: 14 weeks	396 (2 RCTs)	**CARE 3 trial** • Placebo: 2.6% • Cannabidiol: 10 mg/kg/day: 11.0% ◦ Difference: 8.3% (0.3% to 16.3%) • Cannabidiol: 20 mg/kg/day: 25.0% ◦ Difference: 22.4% (12.0% to 32.7%) **CARE 4 trial** • Placebo: 8.2% • Cannabidiol 20 mg/kg/day: 19.8% ◦ O Difference: 11.5% (1.3% to 21.8%)	Low[e]	Cannabidiol 20 mg/kg/day may result in a greater proportion of patients reporting a reduction in drop seizures of 75% or more during the treatment period compared to placebo. Cannabidiol 10 mg/kg/day may result in little to no increase in the proportion of patients reporting a reduction in drop seizures of 75% or more during the treatment period compared to placebo.
Proportion of patients with a 100% reduction in drop seizures from baseline during the treatment period (95% CI)[c] Follow-up: 14 weeks	396 (2 RCTs)	**CARE 3 trial** • Placebo: 0% • Cannabidiol: 10 mg/kg/day: 0% ◦ Difference: NE • Cannabidiol: 20 mg/kg/day: 0% ◦ Difference: NE **CARE 4 trial**	Low[f]	Cannabidiol 10 mg/kg/day and cannabidiol 20 mg/kg/day may result in no difference in the proportion of patients reporting a 100% reduction in drop seizures during the treatment period compared to placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• Placebo: 0% • Cannabidiol 20 mg/kg/day: 0% ◦ Difference: NE		
Seizure freedom				

Change in the mean (SD) number of drop seizure–free days during the treatment period (95% CI)[c]
Follow-up: 14 weeks
	396
	(2 RCTs)
		CARE 3 trial
		• Placebo: 2.3 (SD = 5.1) days
		• Cannabidiol: 10 mg/kg/day: 5.5 (SD = 6.7) days
		  ◦ Difference: 3.3 (1.2 to 5.5) days
		• Cannabidiol: 20 mg/kg/day: 6.8 (SD = 8.2) days
		  ◦ Difference: 4.6 (2.5 to 6.8) days
		CARE 4 trial
		• Placebo: 3.1 (SD = 7.8) days
		• Cannabidiol 20 mg/kg/day: 5.8 (SD = 7.4) days
		  ◦ Difference: 2.7 (0.7 to 4.7) days
			Moderate[g]	Cannabidiol 10 mg/kg/day and cannabidiol 20 mg/kg/day may result in a greater number of seizure-free days during the treatment period compared to placebo.

HRQoL				

Change in mean (SD) overall QOLCE score from baseline to end of treatment (95% CI)[c]
Follow-up: 14 weeks
	171
	(2 RCTs)
		CARE 3 trial
		• Placebo: 16.3 (SD = 30.10)
		• Cannabidiol: 10 mg/kg/day: 7.7 (SD = 12.9)
		  ◦ Difference: 1.6 (−4.5 to 7.8)
		• Cannabidiol: 20 mg/kg/day: 1.0 (SD = 11.9)
		  ◦ Difference: −5.1 (−11.4 to 1.2)
		CARE 4 trial
		• Placebo: 3.9 (SD = 11.5)
		• Cannabidiol 20 mg/kg/day: 7.1 (SD = 16.9)
		  ◦ Difference: 3.7 (−3.3 to 10.7)
			Very low[h]	Cannabidiol 10 mg/kg/day and cannabidiol 20 mg/kg/day likely result in little to no difference in HRQoL during the treatment period compared to placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens

Change in mean (SD) total QOLIE-31-P scores from baseline to end of treatment (95% CI)[c]
Follow-up: 14 weeks
	65
	(2 RCTs)
		CARE 3 trial
		• Placebo: −0.2 (SD = 14.67)
		• Cannabidiol: 10 mg/kg/day: 7.7 (SD = 12.9)
		  ◦ Difference: 1.6 (−4.5 to 7.8)
		• Cannabidiol: 20 mg/kg/day: 2.7 (SD = 8.07)
		  ◦ Difference: 2.9 (−7.3 to 13.1)
		CARE 4 trial
		• Placebo: −0.2 (SD = 14.67)
		• Cannabidiol 20 mg/kg/day: 5.7 (SD = 13.17)
		  ◦ Difference: 3.6 (−7.0 to 14.3)
			Very low[j]	Cannabidiol 10 mg/kg/day and cannabidiol 20 mg/kg/day likely result in little to no difference in HRQoL during the treatment period compared to placebo.

Inpatient hospitalization due to epilepsy				

Number of patients (%) reporting 1 or more inpatient hospitalizations for seizure during the treatment period[c]
Follow-up: 14 weeks
	396
	(2 RCTs)
		CARE 3 trial
		• Placebo: 6 (7.9%)
		• Cannabidiol: 20 mg/kg/day: 7 (9.2%)
		  ◦ Difference: NE
		• Cannabidiol: 10 mg/kg/day: 6 (8.2%)
		  ◦ Difference: NE
		CARE 4 trial
		• Placebo: 5 (5.9%)
		• Cannabidiol 20 mg/kg/day: 10 (11.6%)
		  ◦ Difference: NE
			Low[j]	It is uncertain if cannabidiol 10 mg/kg/day and cannabidiol 20 mg/kg/day result in a difference in inpatient hospitalization due to epilepsy during the treatment period compared to placebo.

Harms[k]				
SAEs, n (%) Follow-up: 20 weeks	396 (2 RCTs)	**CARE 3 trial** • Placebo: 8 (10.5%) • Cannabidiol 20 mg/kg/day: 13 (15.9%) • Cannabidiol 10 mg/kg/day: 13 (19.4%) **CARE 4 trial**	Moderate[l]	Cannabidiol 10 mg/kg/day and cannabidiol 20 mg/kg/day may result in an increase in SAEs compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• Placebo: 4 (4.7%) • Cannabidiol 20 mg/kg/day: 20 (23.3%)		
Hepatocellular injury, n (%) Follow-up: 20 weeks	396 (2 RCTs)	**CARE 3 trial** • Placebo: 12 (17.1%) • Cannabidiol: 20 mg/kg/day: 17 (20.7%) • Cannabidiol: 10 mg/kg/day: 16 (23.9%) **CARE 4 trial** • Placebo: 13 (15.3%) • Cannabidiol 20 mg/kg/day: 24 (27.9%)	Moderate[m]	Cannabidiol 10 mg/kg/day and cannabidiol 20 mg/kg/day may result in an increase in hepatocellular injury compared with placebo.

CI = confidence interval; HRQoL = health-related quality of life; LGS = Lennox-Gastaut syndrome; MID = minimal important difference; NE = not estimated; NR = not reported; POS = partial onset seizure; QOLCE = Quality of Life in Childhood Epilepsy; QOLIE-31-P = Quality of Life in Epilepsy (version 2); RCT = randomized controlled trial; SAE = serious adverse event; SD = standard deviation.

Note: Study limitations (internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]Rated down 1 level for serious imprecision. In the CARE 3 trial, the 95% CI included the potential for no clinically meaningful benefit. In the absence of an empirically derived MID, a between-group difference of 25% was used as the clinically meaningful threshold based on clinical expert input. Any increase (improvement) not reaching this threshold indicates there is uncertainty in the clinically meaningful treatment effect of cannabidiol compared with placebo. Rated down 1 level for serious imprecision. In the CARE 4 trial, the treatment effect estimates and the lower bounds of the 95% CI for difference between groups include the possibility of a trivial effect (little to no difference) when compared with placebo. In the absence of an empirically derived MID, a between-group difference of 25% was used as the clinically meaningful threshold based on clinical expert input. Any increase (improvement) not reaching this threshold indicates there is uncertainty in the clinically meaningful treatment effect of cannabidiol compared with placebo. Potential to rate down for serious indirectness. Although the certainty of evidence was not rated down for serious indirectness, important concerns regarding how well the evidence applies to patients with LGS in Canada were noted by CADTH. These included the lack of study sites in Canada and representation of patients who had experience with medicinally sourced cannabis. Clinical experts advised that the generalizability of the CARE 3 and CARE 4 trials is difficult to determine because of the rarity of LGS and the variability in individual patient clinical characteristics.

[b]Rated down 1 level for serious imprecision. A 20% to 30% difference in the proportion of patients reporting a reduction in drop seizures from baseline of at least 50% was considered meaningful based on the input from the clinical experts. The observed point estimate just met the lower bounds of the MID suggested by the clinical expert. The 95% CI of the point estimates were wide. Potential to rate down for serious indirectness. Although the certainty of evidence was not rated down for serious indirectness, important concerns regarding how well the evidence applies to patients with LGS in Canada were noted by CADTH. These included the lack of study sites in Canada and representation of patients who had experience with medicinally sourced cannabis. Clinical experts advised that the generalizability of the CARE 3 and CARE 4 trials is difficult to determine because of the rarity of LGS and the variability in individual patient clinical characteristics.

[c]Statistical testing for this outcome was not adjusted for multiplicity. The results are considered as supportive evidence.

[d]Rated down 1 level for serious imprecision. In the absence of an empirically derived MID, a 20% to 30% difference was used as the clinically meaningful threshold based on clinical expert input. Any increase (improvement) not reaching this threshold indicates there is uncertainty in the clinically meaningful treatment effect of cannabidiol compared with placebo. In the CARE 3 trial, the point estimate and 95% CI are less than the 20% threshold. In the CARE 4 trial, the point estimate just meets the 20% threshold, while the lower bounds of the 95% CI fall under the threshold. Potential to rate down for serious inconsistency. The results of the CARE 3 and CARE 4 trials are different with the effect estimate and lower 95% CI found under the threshold in CARE 3. Given that the estimate is close to the 20% threshold provided by the clinical expert, there was no rating down for inconsistency. Potential to rate down for serious indirectness. Although the certainty of evidence was not rated down for serious indirectness, important concerns regarding how well the evidence applies to patients with LGS in Canada were noted by CADTH. These included the lack of study sites in Canada and representation of patients who had experience with medicinally sourced cannabis. Clinical experts advised that the generalizability of the CARE 3 and CARE 4 trials is difficult to determine because of the rarity of LGS and the variability in individual patient clinical characteristics.

[e]Rated down 1 level for serious inconsistency. The point estimate in the CARE 4 trial is lower than that estimated in the CARE 3 trial. Rated down 1 level for serious imprecision. In the absence of an empirically derived MID, a between group difference of 15% to 20% was used as the clinically meaningful threshold based on clinical expert input. Any increase (improvement) not reaching this threshold indicates there is uncertainty in the clinically

meaningful treatment effect of cannabidiol compared with placebo. In the CARE 4 trial, the point estimate and 95% CI are less than the 15% threshold. Potential to rate down for serious indirectness. Although the certainty of evidence was not rated down for serious indirectness, important concerns regarding how well the evidence applies to patients with LGS in Canada were noted by CADTH. These included the lack of study sites in Canada and representation of patients who had experience with medicinally sourced cannabis. Clinical experts advised that the generalizability of the CARE 3 and CARE 4 trials is difficult to determine because of the rarity of LGS and the variability in individual patient clinical characteristics.

[f]Rated down 2 levels for serious imprecision based on zero events (responders) in both treatment groups. Potential to rate down for serious indirectness. Although the certainty of evidence was not rated down for serious indirectness, important concerns regarding how well the evidence applies to patients with LGS in Canada were noted by CADTH. These included the lack of study sites in Canada and representation of patients who had experience with medicinally sourced cannabis. Clinical experts advised that the generalizability of the CARE 3 and CARE 4 trials is difficult to determine because of the rarity of LGS and the variability in individual patient clinical characteristics.

[g]Rated down1 level for serious imprecision. The 95% CI of the treatment difference included the point estimate for placebo response. In the absence of an empirically derived MID and no suggested MID from the clinical experts, the null was employed. Potential to rate down for serious indirectness. Although the certainty of evidence was not rated down for serious indirectness, important concerns regarding how well the evidence applies to patients with LGS in Canada were noted by CADTH. These included the lack of study sites in Canada and representation of patients who had experience with medicinally sourced cannabis. Clinical experts advised that the generalizability of the CARE 3 and CARE 4 trials is difficult to determine because of the rarity of LGS and the variability in individual patient clinical characteristics.

[h]Rated down 1 level for serious study limitation. Risk of bias (attrition) due to missing outcome data as results were available for less than 50% of randomized patients in the CARE 3 and CARE 4 trials. Rated down 1 level for serious imprecision. There was no MID estimate specific to the LGS population that was identified or provided by the sponsor. Using the null, the treatment effect and the lower bound of the 95% CI included the potential for decrease (worsening) HRQoL. Potential to rate down for serious indirectness. Although the certainty of evidence was not rated down for serious indirectness, important concerns regarding how well the evidence applies to patients with LGS in Canada were noted by CADTH. These included the lack of study sites in Canada and representation of patients who had experience with medicinally sourced cannabis. Clinical experts advised that the generalizability of the CARE 3 and CARE 4 trials is difficult to determine because of the rarity of LGS and the variability in individual patient clinical characteristics.

[i]Rated down 2 levels for serious study limitation. Risk of bias due to missing outcome data because results were available for only 16% of randomized patients in the CARE 3 and CARE 4 trials. Rated down 1 level for serious imprecision. There was no MID estimate specific to the LGS population that was identified or provided by the sponsor. Applying the MID of 5.19 established for patients with POS, the treatment effect and the lower bound of the 95% CI included the potential for decrease (worsening) HRQoL. Potential to rate down for serious indirectness. Although the certainty of evidence was not rated down for serious indirectness, important concerns regarding how well the evidence applies to patients with LGS in Canada were noted by CADTH. These included the lack of study sites in Canada and representation of patients who had experience with medicinally sourced cannabis. Clinical experts advised that the generalizability of the CARE 3 and CARE 4 trials is difficult to determine because of the rarity of LGS and the variability in individual patient clinical characteristics.

[j]Rated down 2 levels for serious imprecision. In the absence of an empirically derived MID, a between group difference of 10% was used as the clinically meaningful threshold based on clinical expert input. Any increase (improvement) not reaching this threshold indicates there is uncertainty in the clinically meaningful treatment effect of cannabidiol compared with placebo. Difference of treatment effect could not be estimated due to the small number of events. Potential to rate down for serious indirectness. Although the certainty of evidence was not rated down for serious indirectness, important concerns regarding how well the evidence applies to patients with LGS in Canada were noted by CADTH. These included the lack of study sites in Canada and representation of patients who had experience with medicinally sourced cannabis. Clinical experts advised that the generalizability of the CARE 3 and CARE 4 trials is difficult to determine because of the rarity of LGS and the variability in individual patient clinical characteristics.

[k]Between-group differences in harms were not statistically tested.

[l]Rated down 1 level for serious imprecision. Important concerns about the small number of events that precluded estimating a treatment effect. Potential to rate down for serious indirectness. Although the certainty of evidence was not rated down for serious indirectness, important concerns regarding how well the evidence applies to patients with LGS in Canada were noted by CADTH. These included the lack of study sites in Canada and representation of patients who had experience with medicinally sourced cannabis. Clinical experts advised that the generalizability of the CARE 3 and CARE 4 trials is difficult to determine because of the rarity of LGS and the variability in individual patient clinical characteristics.

[m]Rated down 1 level for serious imprecision. Important concerns about the small number of events that precluded estimating a treatment effect. Potential to rate down for serious indirectness. Although the certainty of evidence was not rated down for serious indirectness, important concerns regarding how well the evidence applies to patients with LGS in Canada were noted by CADTH. These included the lack of study sites in Canada and representation of patients who had experience with medicinally sourced cannabis. Clinical experts advised that the generalizability of the CARE 3 and CARE 4 trials is difficult to determine because of the rarity of LGS and the variability in individual patient clinical characteristics.

Long-Term Extension Studies

To inform the longer-term safety and tolerability of cannabidiol as an adjunctive treatment in children and adults with inadequately controlled LGS, the results of 1 open-label extension (OLE) study, the CARE 5 study, were summarized.

Description of Studies

The CARE 5 study was a multicentre, single-arm, OLE, phase III study with the primary objective of evaluating the longer-term safety and tolerability of cannabidiol as an adjunctive treatment, which included children and adults with LGS (N = 366) who had completed the CARE 3 and CARE 4 core studies. The long-term efficacy of cannabidiol as an adjunctive treatment in patients aged 2 years or older with LGS was evaluated as the secondary objective of the CARE 5 study. Patients enrolled in the CARE 5 study received adjunctive cannabidiol in addition to their usual treatment, which consisted of a 2-week titration period, a maintenance period, and a 10-day taper period. Patients were titrated up to 10 mg/kg/day to 20 mg/kg/day cannabidiol using the recommended titration schedule. The participants continued at their 10 mg/kg/day to 20 mg/kg/day dose during the maintenance period. During the maintenance period, dose adjustments by the investigators were permitted if a patient experienced intolerance (dose decrease) or required better seizure control (dose increase) until the optimal dose was achieved. If deemed necessary by the investigator, a maximum dose of 30 mg/kg/day was permitted. Among patients whose dose had been decreased, dose increases were considered, provided there was adequate tolerance. Following the end-of-treatment or withdrawal visit (end-of-treatment visit occurred after a maximum of 6 years of treatment [312 weeks after visit 1], following early withdrawal from the study, or following an unscheduled end-of-treatment visit conducted no earlier than 730 days after visit 1), doses were tapered at home (10% per day for 10 days) until the end-of-taper-period visit. Participants could receive treatment for a maximum of 6 years (312 weeks after visit 1), depending on the protocols used in the country of enrolment.

The CARE 5 study was conducted across 75 sites in 8 countries (Australia, Spain, France, Israel, Netherlands, Poland, UK, and US). Approximately 78% of patients were recruited in the US. The average patient was aged 15.9 years (SD = 9.5) and was concurrently taking 3.4 ASMs (SD = 1.38). Of the 366 patients with LGS enrolled in the study, 66.4% completed the treatment period, 20.5% continued to the taper phase, and 18.3% completed the taper phase.

Efficacy Results

Efficacy end points were analyzed in the safety analysis set. The retention rates for the safety analysis set at weeks 37 to 48 (12 months), 85 to 96, 133 to 144 (36 months), 181 to 192, and 241 to 252 were 82% (299 of 366), 64% (236 of 366), 59% (216 of 366), 6% (22 of 366), and 2% (8 of 366), respectively. Missing data were addressed using the last observation carried forward method.

The proportions of patients with drop seizure–free status at weeks 37 to 48 (12 months), 133 to 144 (36 months), and 253 to 264 (66 months) were 7% (24 of 364), 8% (30 of 364), and 9% (34 of 364), respectively. Median percentage changes from baseline in drop seizure frequency during the same OLE periods from baseline of the core studies were −55.3% (interquartile range [IQR], −83.8% to −16.6%; n = 364), −59.1% (IQR, −85.7% to −15.2%; n = 364), and −59.4% (IQR, −87.1% to −16.0%; n = 364), respectively. Mean percentage

changes in drop seizure frequency during the same periods of the OLE from baseline of the core studies were −34.9% (SD = 82.77; n = 364), −32.3% (SD = 106.11; n = 364), and −30.9% (SD = 127.21; n = 364), respectively. The proportions of patients who experienced a reduction in drop seizure frequency of 50% or greater during the same periods in the CARE 5 study were 53.8% (196 of 364), 56.3% (205 of 364), and 58% (211 of 364), respectively.

Among patients between the ages of 2 and 18 years, the mean change in overall quality of life score as measured by the QOLCE from baseline to last visit was 5.5 (SD = 13.71; n = 152). Among patients aged 19 years and older, the mean change in overall quality of life subscale weighted score on the QOLIE-31-P from baseline to last visit was 6.4 (SD = 28.63; n = 55).

Harms Results

A total of 353 participants (96.4%) with LGS reported experiencing 1 or more AEs during the CARE 5 study. The most common treatment-emergent AEs were convulsion (38.5%), diarrhea (38.3%), and pyrexia (34.4%). SAEs were reported by 157 participants (42.9%) with LGS. The most commonly reported SAEs were convulsion (12%), status epilepticus (11.5%), and pneumonia (7.1%). Discontinuation of treatment due to AEs was reported in 43 participants (11.7%) with LGS. The most common reasons for treatment discontinuation due to AEs were convulsion (1.9%), diarrhea (1.6%), and vomiting (1.4%). A total of 12 patients (3.3%) with LGS died during the study. Among those who died, SUDEP was recorded as the cause of death in 4 patients (1.1%).

Critical Appraisal

The single-group, open-label, nonrandomized design of the CARE 5 OLE study makes interpretation of the long-term efficacy and safety of cannabidiol challenging. The lack of comparison with an active comparator and/or placebo precludes the ability to draw causal inference to assess the relative long-term therapeutic benefit or safety of cannabidiol. Although patient and caregiver self-counts of drop seizures and motor seizures were noted to be reliable based on input from the clinical experts consulted by CADTH for the purpose of this review, self-counting of other types of seizures are not accurate. Results for caregiver-reported and patient-reported outcomes were inconclusive due to the open-label design of the trial and the substantial decline in the number of patients available to provide assessment over time. Moreover, it is uncertain if the sample size (N = 366) was sufficient to detect rare AEs. As enrolment into the CARE 5 study was contingent upon the completion of a core study, thereby excluding patients who discontinued the CARE 3 or CARE 4 trials due to AEs or lack of response, it is possible that patients in the CARE 5 study represent a select population who were more tolerant of cannabidiol. Therefore, response bias cannot be ruled out. Finally, results may be biased due to attrition bias, as approximately one-third of patients did not complete the study, and there was wide variance in follow-up duration for individuals. None of the CARE 5 trial sites were in Canada. Due to the rarity of LGS and a lack of robust population-based studies on LGS in Canada, the clinical experts were unable to determine if the patient population included in the CARE 5 study was reflective of patients in the clinical practice setting across Canada. One clinical expert added that they do not, however, expect patients with LGS living in Canada to differ from those elsewhere. Adherence to

the treatment regimen was not reported and, as such, overall exposure to cannabidiol during the OLE study period is uncertain.

Indirect Comparisons

No indirect treatment comparisons were included in this submission.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps in the evidence from the systematic review were included in this submission.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients aged 2 years or older with LGS inadequately controlled by their current usual care (i.e., patients taking at least 1 ASM who experienced 2 or more drop seizures each week over a 28-day period)
Treatment	Cannabidiol plus usual care (assumed to be comprised of 1 or more ASMs[a])
Dose regimen	2.5 mg/kg twice daily (5 mg/kg/day) for 1 week, then increased to 5 mg/kg twice daily (10 mg/kg/day) to a maximum of 10 mg/kg twice daily (20 mg/kg/day) depending on individual response and tolerability
Submitted price	$1,424.54 per 100 mL bottle
Treatment cost	$5,200 to $83,193 per patient per year, depending on patient weight and dosage
Comparator	Usual care
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (90 years)
Key data source	CARE 3 and CARE 4 clinical trials, CARE 5 extension study
Key limitations	• The full Health Canada–indicated population for LGS was not modelled. Efficacy of cannabidiol plus usual care was based on observations from the CARE 3 and CARE 4 trials, which enrolled patients with 2 or more drop seizures per week over a 28-day period. The cost-effectiveness of cannabidiol among patients with fewer than 2 drop seizures per week is unknown. • The model structure, based on roughly dividing patients into 3 equal groups based on drop seizure frequency and number of seizure-free days per 28-days at baseline from the CARE 3 and CARE 4 trials, does not adequately reflect LGS in clinical practice and does not represent homogeneous health states. • The sponsor's model predicts a gain in QALYs with cannabidiol plus usual care when efficacy and safety inputs are set to be equivalent for cannabidiol plus usual care and usual care alone. The sponsor asserts that this gain is because patients who discontinue cannabidiol will be unlikely to experience the same seizure burden as patients who have never received cannabidiol; no data were provided to support this assumption.

Component	Description
	• The long-term relative effectiveness of cannabidiol plus usual care compared to usual care alone is highly uncertain owing to the use of data from the CARE 5 long-term extension study to inform the effectiveness of cannabidiol after the first 3 months of treatment and the assumption that patients who receive cannabidiol plus usual care will remain in the same health state from cycle 10 until death or discontinuation. Because the CARE 5 study enrolled patients who had completed the pivotal RCTs (the CARE 3 and CARE 4 trials), it is possible that the CARE 5 study represents an enriched population of patients who were benefiting from cannabidiol in the RCTs. Approximately 98% of the incremental benefit associated with cannabidiol was accrued after the pivotal trials on the basis of data from the CARE 5 study and extrapolation. • The health state utility values adopted by the sponsor for patients with LGS are highly uncertain and may not reflect the preferences of patients with LGS in Canada. The majority of incremental QALYs gained with cannabidiol plus usual care were accrued by caregivers, not patients with LGS. • The acquisition costs for cannabidiol were likely underestimated, as the sponsor assumes that all patients will receive a cannabidiol maintenance dose of 10 mg/kg/day despite the Health Canada monograph indicating that patients may receive up to 20 mg/kg/day based on individual treatment response and tolerability. Efficacy data for cannabidiol in the sponsor's model reflect patients from the CARE 3 and CARE 4 trials who were randomized to receive either 10 or 20 mg/kg/day, and from the CARE 5 extension study who received, on average, 24 mg/kg/day. • No uncertainty was incorporated for transitions between health states, which is inappropriate because it does not consider variability in treatment response. Transitions between health states that were not observed in the CARE 3, CARE 4, and CARE 5 studies were assumed by the sponsor to be impossible, which lacks face validity. • The impact of AEs was not adequately considered, owing to the assumption that all serious AEs have the same impact on HRQoL, the use of different incidence thresholds for cannabidiol plus usual care vs. usual care alone, and the lack of consideration of AEs experienced by patients who received 20 mg/kg/day in the CARE 3 and CARE 4 trials. • The survival benefit predicted by the sponsor in their submitted model for cannabidiol plus usual care compared to usual care alone is uncertain and has not been shown in clinical trials.
CADTH reanalysis results	• In the CADTH base case, CADTH adopted an alternate set of health state utility values, excluded the impact of cannabidiol on caregivers, adopted a higher mean dose of cannabidiol, used mean patient weights in the calculation of cannabidiol costs, and assumed that the long-term discontinuation rates for patients who were not seizure-free on cannabidiol plus usual care in cycles 10+ would continue at the rates used for cycles 2 to 9. CADTH was unable to address the remaining limitations. • Results of the CADTH base case suggest that cannabidiol plus usual care is more costly (incremental costs: $200,241) and more effective (incremental QALYs: 1.07) than usual care alone, resulting in an ICER of $186,373 per QALY gained. A price reduction of 71% for cannabidiol would be required for cannabidiol plus usual care to be cost-effective compared to usual care alone at a willingness-to-pay threshold of $50,000 per QALY gained.

AE = adverse event; ASM = antiseizure medication; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LGS = Lennox-Gastaut syndrome; LY = life-year; PSM = partitioned survival model; QALY = quality-adjusted life-year; vs. = versus.

[a]Usual care was assumed by the sponsor to include the following ASMs: clobazam, valproic acid, levetiracetam, topiramate, clonazepam, rufinamide, lamotrigine, perampanel, and lacosamide.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis:

- The modelled population does not reflect the full Health Canada indication for LGS, as only patients with drug-refractory LGS were considered eligible for cannabidiol by the sponsor.
- The Non-Insured Health Benefits population was inappropriately calculated.

- The proportion of patients eligible for public drug plan coverage is uncertain and may be underestimated.
- Cannabidiol drug costs are uncertain and likely underestimated.

CADTH reanalyses aligned the eligible population with the Health Canada indication for LGS, adopted a higher maintenance dose of cannabidiol, used mean weight in the calculation of drug costs, and assumed 100% adherence to treatment. In the CADTH base case, the budget impact of reimbursing cannabidiol for the treatment of seizures associated with LGS is expected to be $3,868,277 in year 1, $10,489,767 in year 2, and $15,071,851 in year 3, for a 3-year total of $29,429,895. If the reimbursement of cannabidiol is restricted to patients with drug-refractory LGS, the 3-year budget impact of reimbursing cannabidiol is expected to be $27,853,385. The estimated budget impact is highly sensitive to the price of cannabidiol.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, and Dr. Peter Zed.

Meeting date: February 28, 2024

Regrets: One expert committee member did not attend.

Conflicts of interest: None

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