Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

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.

Recommendation: Reimburse with Conditions

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Recommendation

The CADTH 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 [N=225] and CARE 4 [N=171] trials) demonstrated that treatment with cannabidiol (at 10 mg/kg/day and 20 mg/kg/day doses), when added on to one 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% 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 (WTP) threshold for patients two years of age or older with LGS who 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 who meet the following criteria: 1.1. 2 years of age or older 1.2. Currently taking 1 or more ASMs at stable doses for at least 4 weeks prior to initiation	Evidence from the CARE 3 and CARE 4 trials demonstrated that treatment with cannabidiol resulted in a reduction in median percentage change in drop seizure frequency in patients aged 2 to 55 years and currently receiving at least one 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 prior to 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. Prescribing and monitoring of cannabidiol for LGS should be limited to adult and pediatric neurologists with expertise in the	Accurate diagnosis and management of patients with LGS-associated seizures is important to ensure that cannabidiol is prescribed only for appropriate patients,	—

Reimbursement condition	Reason	Implementation guidance
diagnosis and management of patients with LGS.	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 prior to 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.	—
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 = anti-seizure 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 old 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), when compared to placebo. CDEC discussed that although cannabidiol resulted in 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 50% reduction from baseline in the frequency of drop of seizures per 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%), when compared to placebo. The clinical experts considered a 20% to 30% between group difference in the proportion of patients reporting al lest 50% reduction in drop seizure from baseline of as a clinically meaningful difference. The GRADE assessment of the evidence showed with a moderate certainty that 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 seizure 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 prior to the trial entry (a 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) for cannabidiol 20 mg/kg/day group in the CARE 4 trial to 86.9 seizures (range, 14.0 to 7494.0) for the placebo group in the CARE 3 trial. CDEC concluded that the benefit for patients with less 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 non-motor seizures can be difficult to detect and therefore the frequency of motor-related seizures (i.e., drop seizures) are more objective for assessing anti-seizure medication effects. In the CARE 3 and CARE 4 trials, the mean number of drop seizure-free days ranged 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 due to 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 discussed that cannabidiol did not meet the needs for correcting 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

Lennox-Gastaut syndrome (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 3-5 years) in developmental normal infants 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 which includes tonic (stiffening of the body, upward eye gaze, dilated pupils, and altered breathing patterns) and atypical absence (staring spells) seizures, followed by myoclonic jerks (sudden muscle jerks), tonic/atonic (brief loss of muscle tone) “drops” and generalized tonic-clonic (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 14 times higher the US general population. Currently, LGS is diagnosed using clinical criteria, there is no specific diagnostic test or biologic markers for the diagnosis of LGS. Lennox-Gastaut syndrome affects between 3 to 10 per cent of children with epilepsy, more commonly in males. The peak age for onset is between 3 to 5 years of age with extreme incidence occurring in the 1st 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-on to other antiseizure medications (ASMs). While lamotrigine is available through the Ontario Drug Benefit (ODB) program, access to rufinamide must be obtained through the Exceptional Access Program (EAP). In addition to antiseizure medications, most patients are also managed using enteral medications; dietary therapies such as ketogenic, modified Atkins, or low-glycemic-index diets; and neuromodulation with vagus nerve stimulation (VNS) or deep brain stimulation, and non-resective 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 licensed producer (so-called ‘artisanal CBD’ 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 (DS) and tuberous sclerosis complex (TSC) in patients 2 years of age 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-blinded, 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 (CARE 5) in patients with a clinical diagnosis of LGS associated seizure who had completed the pivotal studies (CARE 3 and CARE 4).
- Patients’ perspectives gathered by 1 patient group, Canadian Epilepsy Alliance.
- 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 Canadian Epilepsy Alliance (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 across in social, work, and educational settings. Patients often experience depression and anxiety upon initial diagnosis, and continuously suffer from these conditions when anti-seizure medications stop working. Caregivers and family members are also impacted by epilepsy as their lives revolve around the seizures. Anxiety among caregivers is common as they worry about when the next seizure will occur and the consequences of the epilepsy, or how to navigate social gatherings (e.g., a young patient gets invited to a birthday party). In addition, caregivers often experience compassion fatigue since they cannot leave the patient alone and are often sleep deprived due to sleep interruptions or anxiety, while living with many unpleasant side effects of medications their loved are taking (e.g., mood swings, sexual dysfunction, suicidal thoughts, memory loss, fatigue, exhaustion, etc.) Both patients and caregivers emphasized the importance of treatment that results in seizure freedom. However, patients and caregiver noted that they would accept a treatment that resulted in a reduction in the absolute number of seizures as even a reduction in seizure can potentially improve overall quality of life. Of note, since patients with intractable epilepsy are very often un- or under-employed, not covered under employer-funded insurance plans, and have restricted income, most drug to treat their epilepsy are inaccessible. Accordingly, the CEA stressed the importance of new medications placed on the Provincial formulary so the 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. Among the available treatment options, overall prognosis of LGS remain unfavourable and not all patients respond to 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 treatment as symptom management treatment. The clinical experts opined that cannabidiol could be combined with 1 or 2 first line antiseizure agents. The clinical experts also felt that it would be reasonable to require adequate trials of 1 or 2 other antiseizure medications prior to 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 are most likely to benefit from cannabidiol. Patients who have failed to respond to multiple anti-seizure medication are generally less likely to respond to the next anti-seizure medication; however, these are the patients who are most in need of novel therapies. The clinical experts suggest that patients should be screened for treatment according to clinician's judgement based on seizure characterization and frequency, etiology investigation, and previous antiseizure medication trialed, along with EEG interpretation. Based on clinical experts' input, a clinically meaningful response to treatment in epilepsy is assessed as the median reduction in seizure frequency over 28-day periods, seizure reduction by 50% or greater 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 are important secondary outcomes. Based on 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 for cannabidiol for LGS should be limited to paediatric 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 – CARE 3 and CARE 4 – evaluated the efficacy and safety of cannabidiol and usual care against usual care. From the comparator table, lamotrigine was missing. Lamotrigine 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 rufinamide.	Comment from the drug programs to inform CDEC deliberations. The CADTH review team notes that lamotrigine is specially indicated for LGS and is 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 CARE 3 and CARE 4, patients were required to fail more than 1 ASM. Patients were required to be stable on one or more ASMs. A task force of the International League Against Epilepsy recommended replacing the term "intractable" with "drug-resistant" epilepsy and proposed that "drug-resistant" be defined as the failure of adequate trials of two tolerated, appropriately chosen and administered antiseizure medications (whether as monotherapy or in combination) to achieve seizure freedom. (Up-to-date, accessed October 23, 2023)	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: (a) presence of multiple seizure types (i.e., tonic, atonic and tonic-clonic); (b) abnormal EEG patterns of slow spike-wave complexes; and (c) moderate to severe cognitive impairment; and • In CARE 3 and CARE 4, required equal or greater than 8 drop seizures per 28-day period. Should all 3 abovementioned 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 impairments 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 less than 8 LGS-associated seizures per 28 days remains unknown.
In CARE 3 and CARE 4, patients were required to have documented failure on more than 1 ASM, and currently stable on 1 or more ASM. To be eligible for cannabidiol, should patients be	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 CARE 3 and CARE 4 (i.e., treatment failure on

Implementation issues	Response
required to meet the definition of treatment-resistant epilepsy (failure of 2 or more ASMS) similar to rufinamide?	more than one 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 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 to one antiseizure agent.
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 LGS patients, as per the clinician judgement.
In most jurisdictions, rufinamide receives indefinite coverage once approved. No renewal criteria was 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 manufacturer is: • Initial dose 5 mg/kg/day for 1 week • Maintenance dose 10 mg/kg/day up to a max 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 100mg/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 within some regions.	Comment from the drug programs to inform CDEC deliberations.
Patients were excluded from CARE 3 and CARE 4 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 challenging medical condition 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 only or requirement of a credit card for purchase • Physical labeling 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 50mg/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 that 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 is vulnerable, often presenting with intellectual and physical disabilities. Communicating and reporting of side effects may be challenging in this population. Patients in CARE 3 and CARE 4 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 heavier and/or older patients. The price of cannabidiol by weight is as follows:
 	
• **20 Kg (44 lbs)**
  ○ 10 mg/kg/day = $28 per day
  ○ 20 mg/kg/day = $56 per day
• **40 Kg (88 lbs)**
  ○ 10 mg/kg/day = $56 per day
  ○ 20 mg/kg/day = $112 per day
• **80 Kg (176 lbs)**
  ○ 10 mg/kg/day = $112 per day
  ○ 20 mg/kg/day = $224 per day
 	
The price for the comparator drugs:
• Lamotrigine (adult) 400 mg/day is $6.60 per day or $2,409 annually
• Rufinamide [b] (adult-max dose) 800 mg/day is $7.98 per day or $2,912 annually.
	Comment from the drug programs to inform CDEC deliberations.

Cannabidiol is an adjunctive therapy, and therefore, the cost of other ASMs need to be considered.	Comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
The cost of cannabidiol submitted by the manufacturer 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 = anti-seizure medication; CDEC = Canadian Drug Expert Committee; CYP2C19 = cytochrome P450 2C19; CYP3A4 = cytochrome P450 3A4; ECG = electrocardiography; 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: CARE 3 and CARE 4.

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

In CARE 3, 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 CARE 4, 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 CARE 3 and CARE 4 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 one or more background ASMs.

The primary efficacy end point for both CARE 3 and CARE 4 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 an attack or spell (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 patient's head on a surface. The key secondary outcome of interest was the number of patients considered treatment responders defined as achieving a 50% reduction in drop seizures at the end of the treatment period. Other outcomes that were assessed in CARE 3 and CARE 4 included in the CADTH report included: proportions of patients experienced a 25%, 75% and 100% reduction in drop seizure at the end of the treatment period, number of inpatient hospitalizations due to epilepsy, and health-related quality of life as assessed by the Quality of Life in Childhood Epilepsy (QOLCE; for patients aged 2–18 years) or Quality of Life in Epilepsy, version 2 (QOLIE-31-P; for patients aged 19 years and older) score, and number of drop seizure-free days.

In CARE 3, the mean age of patients enrolled in the trial was 16.01 years (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 (SD, 9.26) in the pooled placebo group. In CARE 3, 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 7494.0) compared to the cannabidiol 20 mg/kg/day group (median, 85.53; IQR, 13.0 to 1092.0) and the pooled placebo group (median, 80.25; IQR, 8.7 to 1278.3). The proportion of patients reporting convulsive seizures lasting greater than 30 minutes was higher in the cannabidiol 20 mg/kg/day group (10.5%) compared to the cannabidiol 10 mg/kg/day (2.7%) and the pooled placebo groups (3.9%). The mean number of prior ASMs was approximately 7 and the mean number of current ASMs being used at baseline was almost 3 across treatment groups.

In CARE 4, 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 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 3174.6) 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 almost 3 across treatment groups.

Efficacy Results

Percentage change from baseline in drop seizure frequency

At the end of the 14-week treatment period in CARE 3, 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 CARE 4, a reduction in the median percentage change in drop seizure frequency was associate 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 equal or greater than 50%

In CARE 3, 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 CARE 4, 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 equal or greater than 25%

In CARE 3, 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 CARE 4, 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 equal or greater than 75%

In CARE 3, 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 CARE 4, 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 achieved a 100% reduction in drop seizure frequency during the treatment period in either CARE 3 or CARE 4.

Number of inpatient hospitalization due to epilepsy

In CARE 3, the number of patients with 1 or more inpatient hospitalization 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 CARE 4, the number of patients with 1 or more inpatient hospitalization due to epilepsy was 10 (11.6%) and 5 (5.9%) in the cannabidiol 20 mg/kg/day and volumed-matched placebo group, respectively.

QOLCE for patients aged 2 to 18 years

In CARE 3, overall QOLCE scores were available for 33 (43.4%) patients in the cannabidiol 20 mg/kg/day group, 36 (49.3%) patients in the cannabidiol 10 mg/kg/day group, and in 38 (50%) patients 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 (15.4), and 41.4 (SD, 16.1), respectively. The adjusted mean treatment difference in change from baseline in overall QOLCE scores between 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 CARE 4, overall QOLCE scores were available for 26 (30.2%) and 38 (44.7%) patients 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 CARE 3, total QOLIE-31-P score were available for 13 patients in the cannabidiol 20 mg/kg/day group, 14 patients in the cannabidiol 10 mg/kg/day group and in 10 patients in the pooled placebo group. At baseline, the total mean QOLIE-31-P scores were 50.2 (16.6) in the cannabidiol 20 mg/kg/day group, 56.0 (19.2) in the cannabidiol 10 mg/kg/day group and 62.5 (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, -.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 CARE 4, total QOLIE-31-P scores were available for 14 (16.3%) patients in the cannabidiol 20 mg/kg/day group and 14 (16.5%) patients 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 who completed the assessment.

Drop seizure-free days

In CARE 3, 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 (95% CI, 1.2 to 5.5).

In CARE 4, 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 mean increase of 2.7 days (95% CI, 0.7 to 4.7) days of seizure-free 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 CARE 3 and CARE 4: sudden unexpected death in epilepsy (SUDEP) rate, employment, and HRQoL of caregivers.

Harms Results

Adverse Events

In CARE 3, at least 1 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 in 72.4% of patients in the pooled placebo groups.

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

Serious Adverse Events

In CARE 3, at least 1 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 in 10.5% of patients in the pooled 20 mg/kg/day and 10 mg/kg/day placebo groups.

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

Treatment Discontinuation Due to Adverse Events

In CARE 3, 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 in 1.3% of patients in the pooled placebo group.

In CARE 4, 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 CARE 3. In CARE 4, 1 (1.2%) death 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 ALT and AST, bilirubin elevation and serum transaminase elevation) and gastrointestinal disorders (i.e., diarrhea, vomiting, and constipation)

In CARE 3, 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 CARE 3: 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 CARE 4, 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; 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 multicenter, randomized, double-blinded phase III RCTs. In both trials, patients were randomized centrally using 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 CARE 3 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. Patients in the placebo group were split in half to receive either the 20 mg/kg/day placebo or the 10

mg/kg/day placebo, and the 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 greater 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 unknow if the above-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 CARE 3, 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 EPIDIOLEX 20 mg/kg/day was compared to placebo 20 mg/kg/day (and same for the 10 mg/kg/day dose) was similar to that for the doses versus the pooled placebo response. In CARE 4, 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 CARE 3, 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% vs. approximately 3%). The higher discontinuation rate in the cannabidiol 20 mg/kg/day group appeared to be driven by adverse events. In CARE 4, 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% vs. 1.2%). The higher discontinuation rate in the cannabidiol 20 mg/kg/day group appeared to be driven by adverse events. The application of the MNAR assumption and sensitivity analysis exploring missing efficacy results due to treatment discontinuation suggests that bias due to uneven discontinuation was unlikely.

In both CARE 3 and CARE 4, all efficacy outcome measures were to be completed by the caregiver. To maintain consistency, the same caregiver, if the 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 investigational product, concomitant medications, and adverse event. Based on input from the clinical experts, patient and parent or caregiver report of seizures tend to be accurate for motor seizure; however, are not very reliable or accurate for non-motor seizure. Of note, seizure diaries are the standard method of collecting data for clinical trials and the ILAE recommends the use of dairies for collecting seizure frequency data.[19] Both CARE 3 and CARE 4 assessed HRQoL – outcomes deemed important by the patients and clinicians – using validated and reliable instruments: 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 conclusion based on the HRQoL outcomes are limited since the QOLCE and the QOLIE-31-P were not part of the hierarchical testing procedure, and the low completion rate across the treatment groups. Total QOLCE scores were available for 47.6% and 36.3% of patients in CARE 3 and CARE 4, respectively, while total QOLI-31-P scores were available for 16.5% and 16.4% of patients in CARE 3 and CARE 4, respectively. Consequently, assessment of HRQoL in both trials are at high risk of attrition bias, although the extent and direction of the bias cannot be determined since it is not clear if those 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 CARE 3 and CARE 4, there is little risk of bias that attrition favoured any one treatment group.

Analysis of efficacy results in CARE 3 and CARE 4 followed a defined statistical analysis plan. The primary and key secondary outcomes were addressed using a hierarchical gate keeping procedure which controlled for Type 1 errors. The sponsor conducted additional sensitivity analysis of the primary efficacy outcome using the per-protocol analysis set, and testing the assumption that missing data was not 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 CARE 3 and CARE 4 were applicable to the patients seen 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 the clinical practice in Canada. Briefly, the clinical experts note that the treatment period in CARE 3 and CARE 4 were long enough to detect a meaningful treatment response on seizures in patients with LGS; however, were uncertain if the treatment response observed can 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 for seizure associated with LGS can be accessed through the medical

cannabis pathway supported by Health Canada, the clinical experts would not impose any sort of wash-out period prior to 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, Grading of Recommendations Assessment, Development and Evaluation (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 (which refers to 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 number 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 from clinical expert opinion. Other targets for the certainty of evidence were the presence or absence (non-null) effect for the number of drop-seizure days, number of inpatient hospitalization due to epilepsy and HRQoL as measured by the QOLCE or QOLIE-31-P.

Results of GRADE Assessments

Error! Reference source not found. summarizes the detailed GRADE summary of findings for cannabidiol versus placebo in the pivotal trials CARE 3 and CARE 4 of patients 2 years of age and older with LGS. For the GRADE assessments, findings from CARE 3 and CARE 4 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 10mg/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 RCT)	**CARE 3**
		• 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, -6.7)
		
		CARE 4
		• 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 RCT)	**CARE 3**
		• 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
		• 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 seizure of 50% or more during the treatment period compared to placebo.

Proportion of patients with ≥ 25% reduction in drop seizures from baseline during the treatment period (95% CI) [c]
 	
Follow-up: 14 weeks
	396 (2 RCT)	**CARE 3**
		• Placebo: 43.4%
		• Cannabidiol: 10 mg/kg/day: 63.0%
		  ○ Difference: 19.6% (3.9% to 35.3%)
		• Cannabidiol: 20 mg/kg/day: 61.8%
		  ○ 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
		• Placebo: 43.5%
		• Cannabidiol 20 mg/kg/day: 64.0%
			Moderate [d]	Cannabidiol 20 mg/kg/day may result in a greater proportion of patients reporting a reduction in drop seizure of 25% 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 seizure of 25% or

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		○ Difference: 20.4 (5.8 to 35.1)		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 RCT)	**CARE 3** • 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** • Placebo: 8.2% • Cannabidiol 20 mg/kg/day: 19.8% ○ 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 seizure 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 seizure 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 RCT)	**CARE 3** • Placebo: 0% • Cannabidiol: 10 mg/kg/day: 0% ○ Difference: NE • Cannabidiol: 20 mg/kg/day: 0% ○ Difference: NE **CARE 4** • Placebo: 0% • Cannabidiol 20 mg/kg/day: 0% ○ Difference: NE	Low [f]	Cannabidiol 10 mg/kg/day and cannabidiol 20 mg/kg/day may result in a no difference in the proportion of patients reporting a 100% reduction in drop seizures during the treatment period compared to placebo.
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 RCT)	**CARE 3** • Placebo: 2.3 (5.1) days • Cannabidiol: 10 mg/kg/day: 5.5 (6.7) days ○ Difference: 3.3 (1.2 to 5.5) days • Cannabidiol: 20 mg/kg/day: 6.8 (8.2) days ○ Difference: 4.6 (2.5 to 6.8) days **CARE 4** • Placebo: 3.1 (7.8) days • Cannabidiol 20 mg/kg/day: 5.8 (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.

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

Change in mean (SD) overall QOLCE score from baseline to end of treatment (95% CI) [c]
 	
Follow-up: 14 weeks
	171
	(2 RCT)
		CARE 3
		• Placebo: 16.3 (30.10)
		• Cannabidiol: 10 mg/kg/day: 7.7 (12.9)
		  ○ Difference: 1.6 (-4.5 to 7.8)
		• Cannabidiol: 20 mg/kg/day: 1.0 (11.9)
		  ○ Difference: -5.1 (-11.4 to 1.2)
		
		CARE 4
		• Placebo: 3.9 (11.5)
		• Cannabidiol 20 mg/kg/day: 7.1 (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.

Change in mean (SD) total QOLIE-31-P scores from baseline to end of treatment (95% CI) [c]
 	
Follow-up: 14 weeks
	65
	(2 RCT)
		CARE 3
		• Placebo: -0.2 (14.67)
		• Cannabidiol: 10 mg/kg/day: 7.7 (12.9)
		  ○ Difference: 1.6 (-4.5 to 7.8)
		• Cannabidiol: 20 mg/kg/day: 2.7 (8.07)
		  ○ Difference: 2.9 (-7.3 to 13.1)
		
		CARE 4
		• Placebo: -0.2 (14.67)
		• Cannabidiol 20 mg/kg/day: 5.7 (13.17)
		  ○ Difference: 3.6 (-7.0 to 14.3)
			Very low [i]	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 hospitalization for seizure during the treatment period [c]
 	
Follow-up: 14 weeks
	396
	(2 RCT)
		CARE 3
		• 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
		• Placebo: 5 (5.9)
		• Cannabidiol 20 mg/kg/day: 11.6)
		  ○ Difference: NE
			Low [j]	It is uncertain if cannabidiol 10 mg/kg/day and cannabidiol 20 mg/kg/day results in a difference in inpatients hospitalization due to epilepsy during the treatment period compared to placebo.

		Harms[k]		
Severe adverse events, n (%)	396 (2 (RCT)	**CARE 3** • Placebo: 8 (10.5)	Moderate [l]	Cannabidiol 10 mg/kg/day and cannabidiol 20 mg/kg/day may result in an

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Follow-up: 20 weeks		• Cannabidiol 20 mg/kg/day: 13 (15.9) • Cannabidiol 10 mg/kg/day: 13 (19.4) **CARE 4** • Placebo: 4 (4.7) • Cannabidiol 20 mg/kg/day: 20 (23.3)		increase in SAEs compared with placebo.
Hepatocellular injury, n (%) Follow-up: 20 weeks	396 (2 RCT)	**CARE 3** • Placebo: 12 (17.1) • Cannabidiol: 20 mg/kg/day: 17 (20.7) • Cannabidiol: 10 mg/kg/day: 16 (23.9) **CARE 4** • 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; NE = not estimated; NR = not reported; QOLCE = Quality of Life in Childhood Epilepsy; QOLIE-31-P = Quality of Life in Epilepsy (version 2); RCT = randomized controlled trial

Note: Study limitations (which refers to 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 CARE 3, the 95% IC 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 CARE 4, 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 CARE 3 and CARE 4 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 seizure 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 CARE 3 and CARE 4 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 CARE 3, the point estimate and 95% CI are less than the 20% threshold. In CARE 4, 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 CARE 3 and CARE 4 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 CARE 3 and CARE 4 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 CARE 4 is lower than that estimated in CARE 3. 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 CARE 4, 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 CARE 3 and CARE 4 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 CARE 3 and CARE 4 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 CARE 3 and CARE 4 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 CARE 3 and CARE 4. 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 CARE 3 and CARE 4 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 available for only 16% of randomized patients in CARE 3 and CARE 4. 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 CARE 3 and CARE 4 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 CARE 3 and CARE 4 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 CARE 3 and CARE 4 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 CARE 3 and CARE 4 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 was summarized: CARE 5.

Description of Studies

CARE 5 was a multicenter, single arm, OLE phase III study with the primary objective of evaluating the longer-term safety and tolerability of cannabidiol as adjunctive treatment that included children and adults with LGS (N = 366) who had completed CARE 3 and CARE 4 (Core Studies). The long-term efficacy of cannabidiol as adjunctive treatment in patients aged 2 years and older with LGS was evaluated as the secondary objective of CARE 5. Patients enrolled in CARE 5 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- to 20 mg/kg/day cannabidiol using the recommended titration schedule. The participants continued at their 10 to 20 mg/kg/day dose during the maintenance period. During the maintenance period, dose adjustments by the investigators were permitted should a patient experience intolerance (dose decrease) or require 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' 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 up to a maximum of 6 years (312 weeks after Visit 1), depending on the protocols used in the country of enrollment.

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

Efficacy Results

Efficacy end points were analyzed in the Safety Analysis Set. The retention rates for 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% (299/366), 64% (236/366), 59% (216/366), 6% (22/366), and 2% (8/366), respectively. Missing data were addressed using the last observation carried forward (LOCF) method.

The proportion of patients achieving drop seizure free status at Weeks 37 to 48 (12 months), 133 to 144 (36 months), and 253 to 264 (66 months) were 7% (24/364), 8% (30/364), and 9% (34/364), respectively. Median percentage change 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%, -16.6%; n = 364), -59.1% (IQR, -85.7%, -15.2%; n = 364), and -59.4% (IQR, -87.1%, -16.0%; n = 364), respectively. Mean percentage change 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 proportion of patients who achieved reduction in drop seizure frequency of 50% or greater during the same periods in CARE 5 was 53.8% (196/364), 56.3% (205/364), and 58% (211/364), respectively.

Among patients between the ages of 2 to 18 years, the mean change in overall quality of life score as measured by the QOLCE 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 QOLIE-31-P from baseline to Last Visit was 6.4 (SD, 28.63; n = 55).

Harms Results

A total of 353 (96.4%) participants with LGS reported experiencing 1 or more AEs during CARE 5. The most common TEAEs were convulsion (38.5%), diarrhea (38.3%), and pyrexia (34.4%). SAEs were reported by 157 (42.9%) participants with LGS. The most commonly reported SAEs were convulsion (12%), status epilepticus (11.5%), and pneumonia (7.1%). Discontinuation of treatment due to AEs were reported in 43 (11.7%) participants with LGS. The most common reasons for treatment discontinuation due to AEs

were convulsion (1.9%), diarrhea (1.6%), and vomiting (1.4%). Of a total of 12 (3.3%) patients with LGS died during the study. Among those who did, cause of death due to SUDEP was recorded in 4 (1.1%) patients.

Critical Appraisal

The single-group, open-label, non-randomized, 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-count 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 care giver- 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 enrollment into CARE 5 was contingent on the completion of a Core study, thereby excluding patients who discontinued CARE 3 or CARE 4 due to adverse events or lack of response, it is possible that patients in CARE 5 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 a 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 site 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 CARE 5 were reflective of patients seen 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 two years of age or older with LGS inadequately controlled by their current usual care (i.e., patients taking at least one anti-seizure medication [ASM] who experienced two or more drop seizures each week over a 28-day period)
Treatment	Cannabidiol plus usual care (assumed to be comprised of one or more ASMs[a])
Dose regimen	2.5 mg/kg twice daily (5 mg/kg/day) for one 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)

Component	Description
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 three 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. • 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 CARE 5 enrolled patients who had completed the pivotal RCTs (CARE 3 or CARE 4), it is possible that CARE 5 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 CARE 5 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 CARE 3, CARE 4, and CARE 5 were assumed by the sponsor to be impossible, which lacks face validity. • The impact of adverse events (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 versus 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 2-9. 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

Component	Description
	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.

ASM = anti-seizure medication; ICER = incremental cost-effectiveness ratio; inc. = incremental; LY = life-year; PSM = partitioned survival model; QALY= quality-adjusted life-year.

[a] Usual care was assumed by the sponsor to 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 NIHB 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 three-year total of $29,429,895. If the reimbursement of cannabidiol is restricted to patients with drug-refractory LGS, the three-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