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CADTH Reimbursement Recommendation

Cannabidiol (Epidiolex)

Indication: Use as adjunctive therapy for the treatment of seizures associated with Dravet Syndrome in patients 2 years of age and older
Sponsor: Jazz Pharmaceuticals Canada Inc.
Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Epidiolex?

CADTH recommends that Epidiolex be reimbursed by public drug plans for the adjunctive therapy of seizures associated with Dravet syndrome (DS) in patients aged 2 years or older, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Epidiolex should only be covered to treat patients with seizures associated with DS who experience at least 4 convulsive seizures per 28 days and whose seizures are not adequately controlled with 2 or more other antiseizure medications (ASMs).

What Are the Conditions for Reimbursement?

Epidiolex should only be reimbursed if prescribed by neurologists or pediatric neurologists with experience in the treatment of patients with DS for those with DS who are not receiving other cannabinoid-based medications, and the cost of Epidiolex is reduced. Treatment with Epidiolex should be stopped if the patient does not get beneficial clinical effects a maximum of 6 months after starting, or if the patient has severe side effects or is intolerant to the treatment.

Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials demonstrated that for patients with DS aged between 2 and 18 years old, treatment with Epidiolex, when added on to at least 1 background ASM, resulted in a clinically meaningful reduction in the frequency of convulsive seizures and total seizures, a higher proportion of patients reaching seizure control, and an increase in seizure-free days.
- Although Epidiolex does not impact the underlying condition in DS, the evidence indicated that as adjunctive therapy, it may address the need for a new medication to achieve seizure control and reduce the burden of seizures for patients and their caregivers.
- Based on CADTH's assessment of the health economic evidence, Epidiolex does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Epidiolex is estimated to cost the public drug plans approximately $5.5 million over the next 3 years.

Summary

Additional Information

What Is DS?

DS is a severe form of epilepsy that begins in infancy or early childhood. Patients with DS experience frequent, prolonged, hard-to-treat (treatment-resistant) seizures. DS can also cause developmental delays, speech impairment, problems with coordination (ataxia), reduced muscle tone (hypotonia), sleep disturbances, and other health problems. DS is a rare disease with an estimated prevalence in Canada in 2023 ranging from 1 in 20,000 to 1 in 40,000 individuals, and an estimated mortality rate of 15.84 deaths per 1,000 person years.

Unmet Needs in DS

Patients with DS need new treatments that improve seizure control and health-related quality of life (HRQoL), increase the number of seizure-free days, reduce the need for rescue medications or visits to health care facilities, and decrease seizure burden without affecting mood, cognition, or behaviour.

How Much Does Epidiolex Cost?

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

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that cannabidiol be reimbursed for the adjunctive therapy of seizures associated with DS in patients aged 2 years or older only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two double-blind, placebo-controlled, randomized phase III trials (CARE1B, N = 120, and CARE2, N = 199) demonstrated that treatment with cannabidiol, when added on to at least 1 background ASM (median 3), resulted in added clinical benefit for patients aged between 2 and 18 years who had seizures associated with DS. The CARE1B and CARE2 studies demonstrated that, compared with placebo, 14 weeks of treatment with cannabidiol was associated with a clinically meaningful reduction in the frequency of total seizures (convulsive and nonconvulsive), a higher proportion of patients reaching seizure control (defined as a more than 50% reduction from baseline in seizure frequency), and an increase in seizure-free days. In the CARE1B study, patients in the 20 mg/kg/day cannabidiol group achieved a greater percentage reduction from baseline in convulsive seizure frequency than those receiving placebo (−38.9% versus −13.3%, respectively). The estimated median difference between treatment arms was −22.8% (95% confidence interval [CI], −41.1 to −5.4; P = 0.0123). Similar results were reported in the CARE2 study, with reductions in convulsive seizures from a baseline of −41.2% and −47.0% for cannabidiol 10 mg/kg/day and 20 mg/kg/day, respectively, compared with −24.5% for placebo. The estimated median difference versus placebo was of −15.7% (95% CI −31.3 to 3.7; P = 0.105) for cannabidiol 10 mg/kg/day and −19.9% (95% CI −33.9 to 5.3; P = 0.008) for cannabidiol 20 mg/kg/day. In the CARE1B trial, the proportion of patients who achieved a greater than 50% reduction in seizure frequency was numerically higher in those treated with 20 mg/kg/day of cannabidiol than those in the placebo group after 14 weeks of treatment (42.6% versus 27.1%, respectively; P = 0.078). In the CARE2 trial, compared with placebo, the proportion of patients who achieved at least a 50% reduction in seizure frequency was greater with either the 10 mg/kg/day cannabidiol doses (43.9% versus 26.2%; P = 0.033) or the 20 mg/kg/day cannabidiol doses (49.3% versus 26.2%; P = 0.007). In both trials, increases in the number of convulsive seizure-free days and the percentage reduction in total seizure frequency were observed to favour of treatment with cannabidiol compared with placebo.

Patients identified an unmet need for treatments that improve seizure control and HRQoL, increase the number of seizure-free days, decrease visits to health care facilities and the need for rescue medications, and decrease seizure burden without affecting mood, cognition, or behaviour. Although there was insufficient evidence to evaluate the effects of cannabidiol on HRQoL, CDEC concluded that the available evidence indicated that cannabidiol, as adjunctive therapy, met some patient-identified needs, such as better seizure control and seizure-free days.

Using the sponsor-submitted price for cannabidiol and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for cannabidiol in combination with usual care was $128,062 per quality-adjusted life-year (QALY) compared with usual care alone. At this incremental cost-effectiveness

ratio, cannabidiol plus usual care is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for patients aged 2 years or older with DS 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 reimbursed in patients with seizures associated DS who meet the following criteria: 1.1. those aged 2 years or older who have at least 4 convulsive seizures per month 1.2. those whose seizures are not adequately controlled with 2 or more other antiseizure medications at the time of initiation.	Evidence from the CARE1B and CARE2 pivotal trials demonstrated that treatment with cannabidiol resulted in seizure control benefits in patients with DS with these characteristics.	—
Renewal		
2. 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 patients with seizures associated with DS would ideally be seen as often as every 3 months to monitor treatment and perform any medication adjustments, although most are seen every 6 months.	A specific threshold for defining treatment failure that will apply to all patient is challenging to establish, according to 1 of the clinical experts.
Discontinuation		
3. Treatment with cannabidiol should be discontinued for lack of beneficial clinical effect after an initial maximum of 6 months of treatment, severe toxicity, or treatment intolerance.	This is based on information from the pivotal trials and supported by input from the clinical experts.	—
Prescribing		
4. Cannabidiol for DS should be prescribed by a physician with expertise in the diagnosis and management of patients with DS.	This is to ensure that the treatment is prescribed and safely monitored for the appropriate patients.	—
5. Cannabidiol should not be reimbursed in patients concurrently using cannabis or other cannabinoid-based medications.	The CARE1B and CARE2 pivotal trials excluded patients taking other cannabidiol products. CADTH did not review any evidence demonstrating the safety or potential clinical benefits of the cannabidiol preparation under review in patients who were using other cannabidiol products.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
6. A reduction in price	The ICER for cannabidiol plus usual care is $128,062 when compared with usual care alone. A price reduction of 44% would be required for adjunctive cannabidiol to achieve an ICER of $50,000 per QALY compared to usual care alone.	—

DS = Dravet syndrome; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Discussion Points

- A Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessment of the evidence from the CARE1B and CARE2 pivotal trials found the certainty of effect estimates for seizure control outcomes to be high and moderate. Therefore, CDEC acknowledged that although empirically derived minimal important differences were not identified for these outcomes, the assessment suggests that the results are likely to be clinically meaningful to patients. GRADE assessments rated the evidence for other patient-identified relevant outcomes (such as HRQoL and sleep disruption) as low certainty due to imprecision in the effect estimates. Therefore, the committee could not conclude on the clinical benefit of cannabidiol in improving these outcomes in patients with DS.
- CDEC noted the challenges of establishing an adequate comparator because patients with DS are clinically heterogeneous; thus, therapy commonly comprising various combinations of multiple drugs are based on individual response. Furthermore, no head-to-head comparison of DS interventions was identified.
- CDEC noted that the CARE trials defined clinically beneficial effect as an at least 50% reduction from baseline in the number of seizures per month and acknowledged the clinical experts' submission that the same measure of clinical benefit is commonly applied to ASMs in clinical practice. However, after considering the differences among patients and the unique characteristics of DS (a rare disease with a high mortality rate, treatment-resistant seizures, and reductions in seizure frequency as patients age), the committee decided that a single threshold for clinical benefit or treatment failure may not be practical for all patients. Therefore, CDEC concluded that it should be the place of the attending clinician to determine clinical benefit and/or treatment failure of cannabidiol in patients with DS on a case-by-case basis.
- 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 does not impact the underlying condition in DS but may address the need for a new medication to achieve seizure control and reduce the burden of seizure for patients and their caregivers.

- CDEC discussed the uncertainty in the economic analysis, specifically that in the absence of comparative evidence beyond 14 weeks and uncertainty as to whether the clinical evidence from the CARE trials can be generalized to adults, 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

DS is a very rare form of epilepsy associated with treatment-resistant, lifelong seizures and substantial comorbidities, such as intellectual disability, behaviour, sleep, and gait problems. Epilepsy onset in DS usually occurs within the first year of life with febrile or afebrile clonic and tonic-clonic, generalized, and unilateral seizures in infants without developmental issues. Approximately 70% to 85% of cases with clinical features of DS have mutations of the *SCN1A* gene. The estimated incidence of DS is 1 in 33,000 live births worldwide with a prevalence estimated at 1 in 45,700 children aged younger than 18 years. In Canada, the estimated prevalence is 1 in 40,000.

Diagnosis of DS is based primarily on clinical observations. Confirmatory genetic testing for *SCN1A* can be necessary when there is clinical uncertainty in the diagnosis. Treatment initially includes valproic acid and clobazam, but these are usually insufficient to control seizures. In patients whose disease is refractory to initial therapies, clinicians may add other ASMs, including stiripentol, topiramate, levetiracetam, clonazepam, and rufinamide. Cannabidiol is also recommended as an adjunctive treatment option for patients whose disease does not respond to first-line ASMs.

The objective of this report is to review and critically appraise the evidence submitted by the sponsor on the beneficial and harmful effects of cannabidiol (Epidiolex) oral solution, 100 mg/mL, in the treatment of patients aged 2 years and older with seizures associated with DS.

Cannabidiol has been approved by Health Canada for the treatment of seizures associated with DS in patients aged 2 years and older. Cannabidiol is a plant-derived pharmaceutical formulation available as an oral solution (100 mg/mL) and the dosage recommended in the product monograph is 2.5 mg/kg by mouth twice daily (5 mg/kg/day).

Sources of Information Used by the Committee

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

- a review of 2 randomized clinical trials in patients aged 2 to 18 years of age with DS that is not completely controlled with current antiepileptic medications
- patients' perspectives gathered by 1 patient group, the Canadian Epilepsy Alliance (CEA)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise in diagnosing and treating patients with DS

- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

CADTH received input from the CEA, which is dedicated to the promotion of independence and quality of life for people with epilepsy and their families through support services, information, advocacy, and public awareness. Information for this submission has been gathered by the president of the CEA through consultation with 24 member associations.

The CEA highlighted that individuals with uncontrolled epilepsy are at risk of social isolation and mental illness. The unpredictable nature of seizures and the side effects of medications have negative effects such as anxiety, depression, mood swings, sexual dysfunction, suicidal thoughts, and exhaustion on patients and their family and caregivers. Currently available treatments do not control seizures in all patients. Lack of access to an approved treatment among patients with uncontrolled seizures can result in trying alternative medicines or practices such as cannabis and other unregulated substances. The CEA input mentioned that any reduction in the frequency of seizures can improve quality of life among patients. Because of the frequent seizures, patients with epilepsy syndromes are often unemployed or underemployed with restricted income and without access to employer-funded insurance plans, which limit their access to drugs that are not placed on the provincial formulary.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Two clinical specialists with expertise in the diagnosis and management of DS provided input to this submission. Both agreed that the treatment goals of any therapy for patients with DS include improving seizure control with the improvement of HRQoL, and decreasing seizure burden without affecting the mood, cognition, or behaviour of patients. Other goals include increasing the number of seizure-free days and decreasing visits to health care facilities and the need for rescue medications. The clinical experts mentioned that cannabidiol has the potential for fewer adverse effects when compared to other drugs indicated for this condition. Initially, it was anticipated that cannabidiol would be used after valproic acid and clobazam. The experts mentioned that cannabidiol may be useful in the treatment paradigm in adults as they do not seem to tolerate stiripentol as well as children do; in both populations, more need exists for drugs with fewer side effects and acceptable benefits.

According to the clinical experts, the change over time in seizure frequency, number of seizure-free days, decrease in seizure duration and severity, reduction of status epilepticus, and decreased use of rescue medications are important end points when assessing response to treatment. The experts mentioned that they would consider inadequate improvement in seizure frequency (approximately less than 50% in change from baseline) and intolerable adverse events (AEs) as factors to determine the discontinuation of the medication.

Most patients taking cannabidiol will be treated in outpatient epilepsy clinics. Clinical experts suggest that epileptologists and/or neurologists with expertise in the treatment of DS should monitor response in these patients.

Drug Program Input

Input from the drug plans identified factors pertaining to relevant comparators, considerations for initiation and discontinuation of therapy, generalizability, care provision issues, and system and economic considerations. pERC weighed evidence from the body of evidence and input from the clinical experts consulted by CADTH, which provided advice on the potential implementation issues raised by the drug programs.

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

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Response from clinical experts and presenters
Relevant comparators	
The sponsor notes that the only relevant comparator in this population is usual care because no single combination of ASMs is effective for seizure control in DS. Most patients with DS require 2 or more drugs to achieve reasonable seizure control, and choice of drugs is individualized based on efficacy, side effects, tolerability, and access. Diacomit (stiripentol) is the only ASM with a Health Canada indication for DS. In the CARE1 and CARE2 trials, 35% to 42% of patients took stiripentol concomitantly and 10% to 18% of patients had previously used stiripentol. Other ASMs used in DS are indicated for general epilepsy and are prescribed off-label.	CDEC noted the heterogenous nature of treatments in type and number that patients with DS receive, making the determination of an adequate comparator a challenge. Currently, stiripentol is the only reimbursed comparator indicated for DS in Canada.
Stiripentol is reimbursed in the majority of jurisdictions as a restricted benefit for refractory generalized tonic-clonic seizures in patients with DS. Reimbursement criteria include the use (addition) of stiripentol in combination with clobazam and valproate in patients whose seizures are not adequately controlled with these 2 drugs. British Columbia reimbursement criteria also require documented inadequate response to levetiracetam or topiramate.	CDEC agreed that the use of previous drugs should be a consideration in the reimbursement criteria; however, the committee also noted the lack of evidence for a specific framework or criteria other than the trial inclusion or exclusion criteria.
Considerations for initiation of therapy	
Diagnosis of DS is largely clinical; genetic testing for variants (i.e., *SCN1A*) alone is not sufficient for the diagnosis. Reimbursement criteria for stiripentol only include a diagnosis of Dravet syndrome (without specific criteria around diagnosis). Consider alignment of reimbursement criteria for stiripentol, if appropriate.	Clinical experts and CDEC agreed with the alignment with the stiripentol criteria about the diagnosis of DS.

Drug program implementation questions	Response from clinical experts and presenters
Drug-resistant epilepsy may be defined as failure of adequate trials of 2 tolerated and appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. The inclusion criteria for the CARE1 and CARE2 trials included patients receiving 1 or more ASMs (patients were on approximately 3 ASMs). Based on the Ontario Epilepsy Guidelines, international Dravet-specific guidelines, and Canadian clinical expert opinions, valproate and clobazam are often used initially, but are usually insufficient to control seizures. Patients whose disease is refractory to initial therapies can attempt add-on ASMs, including stiripentol, topiramate, levetiracetam, clonazepam, and rufinamide. Cannabidiol is also recommended as an adjunctive treatment option for patients whose disease does not respond to first-line ASMs. The Health Canada indication and reimbursement criteria for stiripentol include combination treatment with both valproate and clobazam. Would it be appropriate to require patients to be receiving both valproate and clobazam before being eligible for reimbursement of cannabidiol (i.e., similar to stiripentol and aligned with current clinical guidelines)?	According to clinical experts, in most situations patients would have received several treatments before starting cannabidiol; requiring 2 specific treatments will not be needed. CDEC agreed with the clinical experts that specifying 2 medications is not required. However, CDEC added the reimbursement condition requiring patients to have inadequate seizure control on at least 2 other ASMs at the time of initiation with cannabidiol.
Considerations for continuation or renewal of therapy	
Patients with uncontrolled DS typically experience dozens of convulsive seizures each month. Treatment goals focus on balancing optimal seizure control — reducing the length and number of seizures (especially convulsive seizures, which can be associated with sudden unexpected death in epilepsy) and preventing status epilepticus — with side effects and patient quality of life. The primary end point in the CARE1 and CARE2 trials was the percent change from baseline in convulsive seizure frequency. What objective measures are used to assess/monitor therapeutic response in clinical practice?	According to the clinical experts, a specific threshold for treatment failure is challenging to establish. Determining a threshold would need to consider the lack of reduction in the frequency of convulsive seizures, the use of rescue medication, hospital and emergency department visits, the presence of severe adverse events, or treatment intolerance. CDEC agreed with the clinical expert regarding the difficulty of defining a specific threshold for clinical benefit or treatment failure due to the heterogeneity of treatments, variability in the timing and severity of seizure episodes (from 1 per week to hundreds per day), and the value patients and caregivers may have in defining a meaningful benefit or lack thereof (refer to the discontinuation section of this table).
There are no specific renewal criteria for stiripentol.	This was a comment from the drug programs to inform CDEC deliberations.
Considerations for discontinuation of therapy	
How would loss of response be defined?	The clinical experts pointed out that the less than 50% reduction from baseline in seizures frequency used to define a lack of response was a threshold commonly used in clinical trials. However, applying a single threshold to a clinically heterogeneous condition could be challenging. CDEC agreed with the clinical experts, noting that the attending clinician should make the call about clinical benefit

Drug program implementation questions	Response from clinical experts and presenters
	and/or treatment failure (and discontinuation) on a case-by-case basis using professional judgment.
There are no specific discontinuation criteria for stiripentol.	This was a comment from the drug programs to inform CDEC deliberations.
Considerations for prescribing of therapy	
How frequently would patients require the maximum recommended dose of 20 mg/kg/day?	According to the clinical expert, approximately 30% of patients with DS would require the maximum cannabidiol dose of 20 mg/kg/day.
There may be limited access to neurologists in some regions. Stiripentol criteria in most jurisdictions indicate that the drug "must be prescribed by or in consultation with," or the patient "must be under the care of," a neurologist or pediatrician. Consider alignment with prescribing criteria for stiripentol.	This was a comment from the drug programs to inform CDEC deliberations. CDEC agreed that the prescription criteria of cannabidiol should be like that of stiripentol and the patient must be under the care of a neurologist or a pediatrician.
Generalizability	
Patients currently using medicinal cannabis or synthetic cannabinoid-based medications and transitioning to cannabidiol (pharmaceutical) were excluded from the CARE1 and CARE2 trials.	This was a comment from the drug programs to inform CDEC deliberations.
For patients with other forms of treatment-resistant epilepsy, who fall outside the Health Canada indications for cannabidiol, jurisdictions could receive requests for coverage.	This was a comment from the drug programs to inform CDEC deliberations.
Care provision issues	
Due to the risk of hepatocellular injury, ALT, AST, and total bilirubin levels should be obtained at baseline and then at 1, 3, and 6 months after starting treatment and periodically thereafter as clinically indicated, or within 1 month of change in cannabidiol dosing or with changes in other medications that affect liver function.	This was a comment from the drug programs to inform CDEC deliberations. CDEC mentioned that the current evidence suggests that this is not a major issue and that clinicians would monitor any issues of possible toxicities.
System and economic issues	

Concerns regarding the anticipated budget impact and sustainability:
• The list price of Cannabidiol (cannabidiol) 100 mg/mL oral solution is $1,424 per 100 mL bottle.
• According to the sponsor's BIA:
  ◦ the average annual cost for maintenance dosing at 10mg/kg/day is $16,000 (pediatric patient) and $25,000 (adults). A maximum dose of 20mg/kg/day would double the cost.
  ◦ approximately 403, 408, and 412 patients will be treated for DS and 40, 83, and 110 patients will be prescribed cannabidiol in years 1, 2, and 3, respectively
  ◦ the incremental budget impact is $559,000 in year 1, $1.1 million in year 2, $1.5 million in year 3, for a cumulative 3-year budget impact of $3.2 million.
	This was a comment from the drug programs to inform CDEC deliberations.

Drug program implementation questions	Response from clinical experts and presenters
There is a confidential negotiated price for Diacomit (stiripentol).	This was a comment from the drug programs to inform CDEC deliberations.

ALT = alanine-amino transferase; ASM = antiseizure medications; AST = aspartate amino transferase; BIA = budget impact analysis; CDEC = Canadian Drug Expert Committee; DS = Dravet syndrome.

Clinical Evidence

Description of Studies

The body of evidence informing this submission consists of 2 individual studies assessing cannabidiol in patients with DS.

First, the pivotal CARE1 part B study (N = 120 patients) was a phase III, double-blind, placebo-controlled, multicentre, randomized trial evaluating cannabidiol 20 mg/kg/day (n = 61) against placebo (n = 59) as an adjunctive therapy in patients aged 2 to 18 years with DS not completely controlled with current ASMs. The study evaluated seizure frequency per month, proportion of patients with a 50% or greater reduction in convulsive seizure frequency, seizure-free days, status epilepticus, HRQoL scores, sleep disruption, and harms. The time of treatment and assessment was 14 weeks.

Second, the pivotal CARE2 trial was a 3-arm study that evaluated cannabidiol 20 mg/kg/day (n = 67) and 10 mg/kg/day (n = 67) against a placebo group (n = 65). All patients in this study were also aged 2 to 18 years and were receiving multiple therapies for controlling their seizures. This study also evaluated seizure frequency per month, proportion of patients with a 50% or greater reduction in convulsive seizure frequency, seizure-free days, status epilepticus, HRQoL scores, sleep disruption, and harms. The time of treatment and assessment was 14 weeks.

Efficacy Results

Percentage Change From Baseline in Convulsive Seizure Frequency During the Treatment Period

In the CARE1 part B study, patients in the 20 mg/kg/day cannabidiol group achieved a median percentage change from baseline in convulsive seizure frequency during the 14-week treatment period of −38.9% (95% CI, −69.5 to −4.8) versus −13.3% (95% CI, −52.5 to 20.2) for the placebo group. The estimated median difference between the treatment arms was −22.8% (95% CI, −41.1 to −5.4; P = 0.0123).

In the CARE2 study, the median percentage change from baseline during treatment was −41.2% (95% CI, −81 to 3.0), −47.0% (95% CI, −71.4 to −10.5), and −24.5% (95% CI, −51.9 to 4.6) in the cannabidiol 10 mg/kg/day, cannabidiol 20 mg/kg/day, and placebo groups, respectively. The estimated median difference was of −15.7% (95% CI, −31.3 to 3.7) for cannabidiol 10 mg/kg/day versus placebo (P = 0.105) and −19.9% (95% CI, −33.9 to 5.3) for cannabidiol 20 mg/kg/day versus placebo (P = 0.008).

Proportion of Patients With a 50% or Greater Reduction in Convulsive Seizure Frequency From Baseline During the Treatment Period

In the CARE1 part B study, the proportion of patients with a reduction of 50% or more in their baseline convulsive seizure frequency was greater in the cannabidiol group, with 26 of 61 patients (42.6%), than in the placebo group, with 16 of 59 patients (27.1%). The difference in proportions was of 0.155 (95% CI, −0.013 to 0.323) in favour of the intervention. There were twice the odds of achieving this end point in the cannabidiol group compared to placebo (adds ratio [OR] = 2.00; 95% CI, 0.93 to 4.30; P = 0.0784).

In the CARE2 study, the proportion of patients with a reduction of 50% or more in their baseline convulsive seizure frequency was greater in the 10 mg/kg/day group, with 29 of 66 patients (43.9%), and the 20 mg/kg/day group, with 33 of 67 patients (49.3%), than in the placebo group, with 17 of 65 patients (26.2%). The difference in proportion was 0.178 (95% CI, 0.017 to 0.338) in the 10 mg/kg/day group versus the placebo group and 0.231 (95% CI, 0.071 to 0.391) in the 20 mg/kg/day group versus the placebo group. The odds of achieving this end point were higher in both the 10 mg/kg/day group (OR = 2.21; 95% CI, 1.06 to 4.62; P = 0.0332) and the 20 mg/kg/day group (2.74; 95% CI, 1.32 to 5.70; P = 0.0069) when compared to placebo.

Proportion of Patients With a 75% or Greater Reduction in Convulsive Seizure Frequency From Baseline During the Treatment Period

In the CARE1 part B study, the proportion of patients with a reduction 75% or more in their baseline convulsive seizure frequency was greater in the 20 mg/kg/day cannabidiol group than in the placebo group, with 14 of 61 patients (23%) and 7 of 59 patients (11.9%), respectively. The difference in proportions was of 0.111 (95% CI, −0.023 to 0.245) in favour of the intervention. The odds of achieving a 75% or greater reduction was 2.21 (95% CI, 0.82 to 5.95; P = 0.1121) in favour of the 20 mg/kg/day group.

In the CARE2 study, 12 of 67 patients (17.9%) in the 20 mg/kg/day cannabidiol group and 20 of 66 patients (30.3%) in the 10 mg/kg/day cannabidiol group achieved a 75% or greater reduction in convulsive seizure frequency as compared to 4 of 65 patients (6.2%) in the placebo group. The difference in proportion between the 10 mg/kg/day group and the placebo group was 0.241 (95% CI, 0.116 to 0.367); the difference in proportion between the 20 mg/kg/day and the placebo group was 0.118 (95% CI, 0.009 to 0.226). The odds of achieving a 75% or greater reduction was 6.63 (95% CI, 2.12 to 20.73; P = 0.0004) in the 10 mg/kg/day group and 3.33 (95% CI 1.01 to 10.92; P = 0.0468) in the 20 mg/kg/day group when compared to placebo.

Number of Convulsive Seizure-Free Days

In the CARE2 study, the mean number of convulsive seizure-free days increased in all 3 treatment groups, although greater increases were seen in the 10 mg/kg/day and 20 mg/kg/day cannabidiol groups compared with placebo. The treatment difference was in favour of cannabidiol for both groups at 2.4 (95% CI, 1.0 to 3.9; P = 0.0009) between the 10 mg/kg/day group and placebo, and 1.3 (95% CI, −0.1 to 2.8; P = 0.0683) between the 20 mg/kg/day group and placebo.

Percentage Change From Baseline in Total Seizure Frequency During the Treatment Period

In the CARE1 part B study, a greater median percentage change in total seizure frequency was seen in the 20 mg/kg/day cannabidiol group (−28.6; 95% CI, −70.4 to −4.0) compared to the placebo group (−9.0; 95% CI,

−51.4 to 19.6). The median difference between 20 mg/kg/day cannabidiol and placebo was −19.2 (95% CI, −39.3, −1.2; P = 0.0335).

In the CARE2 study, the percentage reduction was 56.4 (95% CI, 47.8 to 63.6) in the 10 mg/kg/day and 47.3 (95% CI, 36.9, 56.0) in the 20 mg/kg/day cannabidiol groups compared to 29.7 (95% CI, 16.0 to 41.1) in the placebo group.

Patients With Status Epilepticus

In both studies, there were few incidents of status epilepticus reported overall during the baseline and treatment periods, with similar rates across all treatment groups. In the CARE1 part B study, there was only 1 case (1.6%) in the 20 mg/kg/day group versus 0 in the placebo group at the end of the treatment period. Similarly, patients in the CARE2 study presented status epilepticus of 3 (4.5%), 9 (13.4%), and 8 (12.3%) in the cannabidiol 10 mg/kg/day, cannabidiol 20 mg/kg/day, and placebo groups, respectively, at the end of treatment.

Health-Related Quality of Life

Patients included in the CARE1 part B and CARE2 studies had a poor quality of life based on the low mean overall Quality of Life in Childhood Epilepsy Questionnaire (QOLCE) scores at baseline. Nonetheless, the adjusted mean differences for all scores in both studies were in favour of cannabidiol treatment 20 mg/kg/day in the CARE1 part B study, with an adjusted mean difference of 1.5 points (95% CI, −3.8 to 6.8; P = 0.576), 3.8 points (95% CI, −0.1 to 7.8; P = 0.058), and 1.8 points (95% CI, −2.2 to 5.8; P = 0.382) in the 10 mg/kg/day, 20 mg/kg/day, and placebo groups in the CARE2 study, respectively.

Sleep Disruption and Function

In the CARE1 part B and CARE2 studies, mean baseline Sleep Disruption Numerical Rating Scale (NRS) scores were similar across the treatment groups. In the CARE1 part B trial, a mean treatment difference in Sleep Disruption NRS score of −0.4 (95% CI, −1.5 to 0.7) was observed, with no evidence of a significant difference between cannabidiol 20 mg/kg/day and placebo. Similarly, in the CARE2 trial, the mean treatment difference in Sleep Disruption NRS score between the 10 mg/kg/day cannabidiol group and the placebo group was 0.0 (95% CI, −0.9 to 0.8) and between the 20 mg/kg/day cannabidiol and placebo groups was −0.1 (95% CI, −0.9 to 0.8).

Mean Epworth Sleep Scale (ESS) scores at baseline were relatively high in both trials in all treatment groups (> 7.1 in the CARE1 part B study and > 7.2 in the CARE2 study). In the CARE1 part B trial, the mean treatment difference in ESS score between the 20 mg/kg/day cannabidiol group and the placebo group was 1.51 (95% CI, −0.18 to 3.19) in favour of placebo (P = 0.078). In the CARE2 trial, the mean treatment difference in ESS score between the 10 mg/kg/day group and the placebo group was −0.55 (95% CI, −1.86 to 0.75; P = 0.404); it was 0.74 (95% CI, −0.57 to 2.05; P = 0.267) between the 20 mg/kg/day group and the placebo group.

Resource Use

In the CARE1 part B study, a total of 6 patients (5%) reported 1 or more inpatient hospitalizations due to epilepsy during the treatment period: 5 patients (8.2%) in the 20 mg/kg/day cannabidiol group and 1 patient (1.7%) in the placebo group. In the CARE2 study, a total of 26 patients (13.1%) reported 1 or more inpatient

hospitalizations due to epilepsy: 8 patients (11.9%) in the 20 mg/kg/day cannabidiol group, 12 patients (18.2%) in the 10 mg/kg/day cannabidiol group, and 6 patients (9.2%) in the placebo group.

The number of patients using rescue medication was overall similar in both studies. In the CARE1 part B trial, 36 patients (59.0%) and 41 patients (69.5%) in the cannabidiol 20 mg/kg/day and placebo groups, respectively, used rescue medication, while in the CARE2 study the numbers of patients using rescue medication in the cannabidiol 10 mg/kg, cannabidiol 20 mg/kg, and placebo groups were 54 (84.4%), 58 (84.1%), and 54 (80%), respectively.

Harms Results

In the CARE1 part B study, 57 of 61 patients (93.4%) in the 20 mg/kg/day cannabidiol group and 44 of 59 patients (74.6%) in the placebo group reported 1 or more AE. In the CARE2 trial, 56 of 64 patients (87.5%) in the 10 mg/kg/day cannabidiol group, 62 of 69 patients (89.9%) in the 20 mg/kg/day cannabidiol group, and 58 of 65 patients (89.2%) in the placebo group reported 1 or more AE. The most common AEs reported in both studies (more than 10% of patients in any treatment group) were somnolence, diarrhea, and decreased appetite.

In the CARE1 part B study, 10 of 61 patients (16.4%) in the 20 mg/kg/day cannabidiol group and 3 of 59 patients (5.1%) in the placebo group reported 1 or more serious adverse events (SAEs). In the CARE2 trial, 13 of 64 patients (20.3%) in the 10 mg/kg/day cannabidiol group, 17 of 69 patients (24.6%) in the 20 mg/kg/day cannabidiol group, and 10 of 65 patients (15.4%) in the placebo group reported 1 or more SAE. The most common SAEs reported in both studies were nervous system disorders, status epilepticus, somnolence, and convulsion. Pneumonia was also a common SAE reported in the CARE2 study. All SAEs were resolved in the CARE1 part B study, while 3 patients in the 20 mg/kg/day cannabidiol group in the CARE2 study had 3 SAEs that were not resolved at the end of the trial.

Patient discontinuation from treatment due to AEs was relatively low, although higher in the 20 mg/kg/day cannabidiol groups in both studies. In the CARE1 part B trial, AEs that led to treatment discontinuation occurred in 9 of 61 patients (14.8%) in 20 mg/kg/day cannabidiol group and in 1 of 59 patients (1.7%) in the placebo group, while in the CARE2 trial, 5 of 69 patients (7.2%) in the 20 mg/kg/day cannabidiol group experienced AEs that led to study discontinuation. No patients in the 10 mg/kg/day cannabidiol group or placebo group withdrew from the study due to AEs and no patient deaths occurred during either study.

Critical Appraisal

The CARE1 part B and CARE2 studies are randomized controlled trials involving an adequate randomization process, with overall balanced distribution of participants to either the cannabidiol or placebo arms. There were some observed baseline imbalances in both studies; however, these were judged to have a low risk of introducing bias. There was good adherence to the intended interventions. There were, however, some imbalances observed in the use of different cointerventions; although these possible deviations could introduce bias, the impact and direction of the bias on the outcomes of interest are uncertain. Some modifying effects from variables were observed (i.e., use of stiripentol, use of clobazam, and geographical location); however, the small number of patients across subgroups in both studies warrants caution for

stating any credible effect modification from any of these variables. There were no instances of meaningful missing outcomes data. In both studies, measurements of the outcomes were appropriate. The blinding of participants and clinical investigators maintained throughout the conduct of the studies mitigates potential biases in this domain. Overall, both studies demonstrated adherence to methodological consistency and minimized risks across all domains assessed for risk of bias for most outcomes when comparing cannabidiol to placebo. Several secondary end points depicting statistically significant results lacked multiplicity control, which carries a risk of false-positives; as a result, cautious interpretation because of the potential for random error is needed.

Overall, patients included in the CARE1 part B and CARE2 trials have baseline characteristics and prognostic factors similar to those encountered in the population of Canada with DS, according to clinical experts consulted by CADTH. There were some concerns of uncertainty on the applicability of the results to adult populations older than aged 18 years because no patients older than aged 18 were included in both trials. However, according to the clinical experts consulted by CADTH, it is unlikely that the response observed in the CARE1 part B and CARE2 studies will be different in terms of beneficial effects and possible harms. There is also uncertainty related to whether the results can be generalized to patients with fewer than 4 seizures per month because patients with such characteristics were not included in these studies. The trials excluded patients using medicinal cannabis or synthetic cannabinoid-based medications and transitioning to cannabidiol (pharmaceutical). This would be a common situation in Canada; however, the clinical experts suggested that though this is an important consideration, it is unlikely to affect the generalizability of the trial results.

The question of whether cannabidiol is more efficacious than other treatments available in Canada for patients with DS (i.e., stiripentol) when added to standard of care is still uncertain. There is no head-to-head comparison of cannabidiol against stiripentol. Furthermore, the standard of care treatments commonly used in patients with DS vary, which makes it difficult to assess this question using indirect comparison as such differences may include issues of inconsistency or intransitivity. With the lack of head-to-head comparisons, and the current evidence at hand, it is difficult to draw strong conclusion on this issue.

Results of GRADE Assessments

The GRADE assessments included an evaluation of the main outcomes considered important by clinicians, patient groups, and stakeholders. The comparisons evaluated in the GRADE assessments of this report were that of cannabidiol 10 mg/kg/day against placebo and cannabidiol 20 mg/kg/day versus placebo. In Table 3 and Table 4, we present the GRADE summary of findings respectively for each comparison.

Table 3: Summary of Findings for Cannabidiol 10 mg/kg/day Versus Placebo for Patients With Dravet Syndrome

Outcome and follow-up	Patients (studies), N	Relative effect	Absolute effects			Certainty	What happens
			Placebo	Cannabidiol 10 mg/kg/day	Difference		
Seizure control							
Median % change from baseline of convulsive seizure frequency Follow-up: 14 weeks	131 (1 RCT)	NA	−24.5%	−41.2% (95% CI, −81.0 to 3.0)	15.7% greater reduction (from 3.7 increase to 31.3 reduction)	Moderate[a]	Cannabidiol 10 mg/kg/day likely reduces the frequency of convulsive seizures from baseline when compared to placebo.
≥ 50% reduction in convulsive seizure frequency from baseline Follow-up: 14 weeks	131 (1 RCT)	OR = 2.21 (95% CI, 1.06 to 4.62)	17/65 (26.2%)	29/66 (43.9%)	178 more per 1,000 (from 17 more to 338 more)	Moderate[b]	Cannabidiol 10 mg/kg/day likely increases convulsive seizure control (≥ 50% reduction from baseline) when compared to placebo.
≥ 75% reduction in convulsive seizure frequency from baseline Follow-up: 14 weeks	131 (1 RCT)	OR = 6.63 (95% CI, 2.12 to 20.73)	12/67 (17.9%)	20/66 (30.3%)	241 more per 1,000 (from 116 more to 367 more)	High	Cannabidiol 10 mg/kg/day increases convulsive seizure control (≥ 75% from baseline) when compared to placebo.
Mean number of convulsive seizure-free days, change from baseline Follow-up: 14 weeks	131 (1 RCT)	NA	1.7	3.9 (SD = 4.8)	MD = 2.4 days more (from 1 more to 3.9 more)	High	Cannabidiol 10 mg/kg/day increases the mean number of convulsive seizure-free days from baseline when compared to placebo.
Median % change from baseline in total seizure frequency Follow-up: 14 weeks	131 (1 RCT)	NA	Change from baseline in the intervention group was −51.9% (95% CI, −79.3 to −14.5) while in the placebo group it was −26.8%. MD was not reported.			Moderate[c]	Cannabidiol 10 mg/kg/day likely reduces the frequency of total seizures from baseline when compared to placebo.
% patients with convulsive status epilepticus change from baseline Follow-up: 14 weeks	131 (1 RCT)	NA	Number with status epilepticus went from 4 of 66 (6.1%) at baseline to 3 (4.5%) at end of treatment in the intervention group; placebo group went from 4 of 65 (6.2%) to 8 (12.3%). Changes from baseline and between-group differences were not reported.			Low[c]	Cannabidiol 10 mg/kg/day may produce little to no difference in the frequency of status epilepticus from baseline when compared to placebo.

Outcome and follow-up	Patients (studies), N	Relative effect	Absolute effects			Certainty	What happens
			Placebo	Cannabidiol 10 mg/kg/day	Difference		
Health-related quality of life							
Adjusted mean change from baseline in QOLCE score Follow-up: 14 weeks	110 (1 RCT)	NA	2.6	6.4 (SD = 10.9)	MD = 3.8 points higher (0.1 lower to 7.8 higher)	Low[d]	Cannabidiol 10 mg/kg/day may produce little to no difference in HRQoL when compared to placebo. The clinical meaningfulness of the results is uncertain.
Sleep disruption							
Change from baseline in mean ESS and 0 to 10 NRS scores Follow-up: 14 weeks	131 (1 RCT)	NA	Mean difference in the Sleep Disruption 0 to 10 NRS scale was 0 (95% CI, −0.9 to 0.8), while the mean difference in ESS score was −0.55 (95% CI, −1.86 to 0.75).			Low[d]	Cannabidiol 10 mg/kg/day may produce little to no difference in the sleep disruption scales when compared to placebo. The clinical meaningfulness of the results is unclear.
Resource utilization							
Rescue medication and hospital days Follow-up: 14 weeks	131 (1 RCT)	NA	In the cannabidiol 10 mg/kg and placebo groups, 54 (84.4%) and 54 (80%) patients, respectively, used rescue medications; 12 (18.2%) and 6 (9.2%) patients, respectively, were hospitalized due to epilepsy.			Low[e]	Cannabidiol 10 mg/kg/day may produce little to no difference in health resource utilization. The clinical meaningfulness of the results is unclear.
Harms							
AEs, SAEs, and harms of special interest Follow-up: 14 weeks	131 (1 RCT)	NA	Number (%) of patients experiencing AEs in the cannabidiol 10 mg/kg/day and placebo groups were, respectively, 56 (87.5%) vs. 58 (89.2%), and SAEs were 13 (20.3%) vs. 10 (15.4%). No patients died.			Low[e]	Cannabidiol 10 mg/kg/day may produce little to no difference in AEs and SAEs. The clinical meaningfulness of the results is unclear.

AE = adverse event; CI = confidence interval; ESS = Epworth Sleepiness Scale; HRQoL = health-related quality of life; MD = mean difference; NA = not applicable; NRS = numerical rating scale; QOLCE = Quality of Life in Childhood Epilepsy Questionnaire; RCT = randomized controlled trial; SAE = serious adverse event; SD = standard deviation; vs. = versus.

[a]Rated down 1 level for imprecision. The target of our certainty is on a nontrivial effect. The 95% CI includes the null and the threshold of a 5% meaningful difference between treatment and placebo, as informed by the clinical experts.

[b]Rated down for imprecision. The target of our certainty is an important benefit. The 95% CI includes the threshold of meaningful difference between treatment and placebo of 20 patients more (or fewer) per 1,000 treated as considered by the clinical experts consulted by CADTH.

[c]Rated down 2 levels for imprecision. No thresholds or CIs were assessed. Based on sample size, the number did not reach a plausible optimal information size.

[d]Rated down 2 levels for imprecision. Based on the target of the certainty of a meaningful effect of the intervention, the 95% CI was considered wide and no threshold of a minimal important difference could be obtained.

[e]Rated down for imprecision. No CIs could be assessed. Rated down due to a small sample size that did not reach a plausible optimal information size.
Source: This comparison was obtained from the CARE2 study assessing the 10 mg/kg/day arm vs. placebo.

Table 4: Summary of Findings for Cannabidiol 20 mg/kg/day Versus Placebo for Patients With Dravet Syndrome

Outcome and follow-up	Patients (studies), N	Relative effect	Absolute effects			Certainty	What happens
			Placebo	Cannabidiol 20 mg/kg/day	Difference		
Seizure control							
Median percent change from baseline of convulsive seizures frequency Follow-up: 14 weeks	252 (2 RCTs)	NA	• **CARE1b study**: placebo arm = 13.3% reduction of convulsive seizures; cannabidiol arm = 38.9% reduction. MD = 22.8% greater reduction (95% CI, 5.4 greater reduction to 41.1 greater reduction) • **CARE2 study**: placebo arm = 24.5% reduction of convulsive seizures; cannabidiol arm = 47% reduction. MD = 19.9% greater reduction (95% CI, 5.3 greater reduction to 33.9 greater reduction)			High	Cannabidiol 20 mg/kg/day reduces the frequency of convulsive seizures from baseline when compared to placebo.
≥ 50% reduction in convulsive seizure frequency from baseline Follow-up: 14 weeks	252 (2 RCTs)	Care 1b: OR = 2.0 (95% CI, 0.93 to 4.30) Care 2: OR = 2.74 (95% CI, 1.32 to 5.70)	• **CARE1b study**: 155 more per 1,000 (from 13 fewer to 323 more) • **CARE2 study**: 231 more per 1,000 (from 71 more to 391 more)			High	Cannabidiol 20 mg/kg/day increases convulsive seizure control (≥ 50% reduction from baseline) when compared to placebo.
≥ 75% reduction in convulsive seizure frequency from baseline Follow-up: 14 weeks	252 (2 RCTs)	Care 1b: OR = 2.21 (95% CI, 0.82 to 5.95) Care 2: OR = 3.33 (95% CI, 1.01 to 10.92)	• **CARE1b study**: 111 more per 1,000 (from 23 fewer to 245 more) • **CARE2 study**: 118 more per 1,000 (from 9 more to 226 more)			Moderate[a]	Cannabidiol 20 mg/kg/day likely increases convulsive seizure control (≥ 75% reduction from baseline) when compared to placebo.
Mean number of convulsive seizure-free days, change from baseline Follow-up: 14 weeks	132 (1 RCT)	NA	**CARE2 study**: MD = 1.3 days more (0.1 fewer to 2.8 more)			Moderate[b]	Cannabidiol 20 mg/kg/day likely increases the frequency of convulsive seizure-free days from baseline than placebo.

Outcome and follow-up	Patients (studies), N	Relative effect	Absolute effects			Certainty	What happens
			Placebo	Cannabidiol 20 mg/kg/day	Difference		
Median percent change in total seizures frequency change from baseline Follow-up: 14 weeks	252 (2 RCTs)	NA	• **CARE1b study**: median difference = 19.2% lower (39.3 lower to 1.2 lower) in favour of cannabidiol • **CARE2 study**: The change from baseline (Q1,Q3) in the intervention group was −52.7% (95% CI, −67.1 to −13.1) while in the placebo group it was −26.8% (95% CI, −58.1 to 7.0). Median difference was not reported.			Moderate[c]	Cannabidiol 20 mg/kg/day likely reduces the frequency of total seizures from baseline when compared to placebo.
Percentage of patients with convulsive status epilepticus, change from baseline Follow-up: 14 weeks	252 (2 RCTs)	NA	• **CARE1b study**: The number of patients went from 0 of 61 at baseline to 1 (1.6%) at end of treatment in the intervention group, while in the placebo group it went from 1 of 59 (1.7%) to 0 patients. • **CARE2 study**: The number of patients went from 6 of 67 (9%) at baseline to 9 (13.4%) at the end of treatment in the intervention group, while in the placebo group it went from 4 of 65 (6.2%) to 8 (12.3%).			Low[d]	Cannabidiol 20 mg/kg/day may produce little to no difference in the frequency of status epilepticus from baseline compared to placebo.
Health-related quality of life							
Adjusted mean change from baseline in QOLCE score Follow-up: 14 weeks	193 (2 RCTs)	NA	• **CARE1b study**: MD = 1.5 points higher in the intervention group (3.8 lower to 6.8 higher) • **CARE2 study**: MD = 1.8 points higher in the intervention group (2.2 lower to 5.8 higher)			Low[e]	Cannabidiol 20 mg/kg/day may produce little to no difference in HRQoL when compared to placebo. The clinical meaningfulness of the results is uncertain.
Sleep disruption							
Change from baseline in mean ESS and 0 to 10 NRS Follow-up: 14 weeks	252 (2 RCTs)	NA	• **CARE1b study**: The mean difference (95% CI) in the sleep disruption 0 to 10 NRS scale was −0.4 (9%% CI, −1.5 to 0.7), while the mean difference in ESS score was 1.51 (95% CI, −0.18 to 3.19). • **CARE2 study**: The mean difference (95% CI) in the sleep disruption 0 to 10 NRS scale was −0.1 (95% CI, −0.9 to 0.8), while the mean difference in ESS score was 0.74 (95% CI, −0.57 to 2.05).			Low[d]	Cannabidiol 20 mg/kg/day may produce little to no difference in the sleep disruption scales when compared to placebo. The clinical meaningfulness of the results is uncertain.

Outcome and follow-up	Patients (studies), N	Relative effect	Absolute effects			Certainty	What happens
			Placebo	Cannabidiol 20 mg/kg/day	Difference		
Resource utilization							
Rescue medication and hospital days Follow-up: 14 weeks	252 (2 RCTs)	NA	• **CARE1b study**: In the intervention and placebo groups, 36 (59.0%) and 41 (69.5%) patients, respectively, used rescue medications; meanwhile, 5 (8.2%) and 1 (1.7%) patients, respectively, were hospitalized because of epilepsy. • **CARE2 study**: In the intervention and placebo groups, 58 (84.1%) and 54 (80%) patients, respectively, used rescue medications; meanwhile, 8 (11.9%) and 6 (9.2%) patients, respectively, were hospitalized due to epilepsy.			Low[d]	Cannabidiol 20 mg/kg/day may produce little to no difference in health resource utilization. The clinical meaningfulness of the results is uncertain.
Harms							
AEs, SAEs, and harms of special interest Follow-up: 14 weeks	252 (2 RCTs)	NA	• **CARE1b study**: At least 1 AE in the intervention and placebo groups was present in 57 (93.4%) and 44 (74.6%) patients, respectively. Meanwhile, SAEs occurred in 10 (16.4%) and 3 (5.1%) patients, respectively. Somnolence occurred in 5 patients vs. 0 patients. Liver enzyme investigations occurred in 4 vs. 1 patients, respectively. • **CARE2 study**: AEs in the intervention and placebo groups occurred in 62 (87.9%) vs. 58 (89.2%) patients, SAEs in 17 (24.6%) vs. 10 (15.4%) patients, liver enzyme investigations in 3 vs. 0 patients, and somnolence in 2 vs. 0 patients, respectively.			Low[d]	Cannabidiol 20 mg/kg/day may produce more AEs, SAEs, cases of somnolence, and investigations of liver enzymes than placebo. The clinical meaningfulness of these results is uncertain.

AE = adverse event; CI = confidence interval; ESS = Epworth Sleepiness Scale; HRQoL = health-related quality of life; MD = mean difference; NA = not applicable; NRS = numerical rating scale; QOLCE = Quality of Life in Childhood Epilepsy Questionnaire; RCT = randomized controlled trial; SAE = serious adverse event; SD = standard deviation; vs. = versus.

[a]Rated down for imprecision. The target of our certainty is an important benefit. The CI crosses a threshold of 20 patients more (or fewer) per 1,000 treated as considered by the clinical experts consulted by CADTH.

[b]Rated down by 1 for imprecision. The target of the certainty is that of any beneficial effect (based on the null). Only 1 study assesses this outcome. No thresholds or CIs were evaluated.

[c]The target of the certainty is that of an important benefit. The lower bound of the CI could include a trivial effect for which a threshold was considered at 5%.

[d]No thresholds or CIs were assessed. Numbers are not optimal to assess if the intervention provides a large or trivial effect; hence, it was rated down 2 levels for imprecision.

[e]Based on the target of the certainty of a meaningful effect of the intervention, the 95% CI was considered wide and no threshold of a minimal important difference could be obtained. The sample size was considered low in relation to a plausible optimal information size.

Source: These results were obtained from the CARE1 part B and CARE 2 studies.

Long-Term Extension Studies

Description of Studies

CARE5 was a multicentre, open-label extension study for patients with DS or Lennox-Gastaut syndrome who had completed the double-blind, placebo-controlled, clinical studies with cannabidiol (the CARE1, CARE2, CARE3, and CARE4 studies). The objective of this open-label extension study was to evaluate the long-term safety, tolerability, and effect on seizures of cannabidiol as adjunctive treatment in children and adults with inadequately controlled DS or Lennox-Gastaut syndrome.

Efficacy Results

During weeks 37 to 48 of treatment, patients with DS experienced a median percentage change of −62.6% from their original study baseline total seizure frequency. The proportion of patients who achieved a 50% or greater reduction in total seizure frequency during weeks 37 to 48 of treatment was 59.3%. Out of all patients with DS, 70.1% experienced a 25% or greater reduction in total seizure frequency, 39.7% experienced a 75% or greater reduction in total seizure frequency, and 6.1% experienced total seizure freedom (100% reduction).

During weeks 37 to 48 of treatment, patients with DS experienced a median percentage change of −54.2% from their baseline convulsive seizure frequency from their original study. The proportion of patients who achieved a 50% or greater reduction in convulsive seizure frequency during weeks 37 to 48 of treatment was 52.3%. Out of all patients with DS, 67.8% experienced a 25% or greater reduction in convulsive seizure frequency, 34.6% experienced a 75% or greater reduction in convulsive seizure frequency, and 7.9% experienced convulsive seizure freedom (100% reduction). During the last 12 weeks of treatment, 4.5% of patients with DS reported convulsive seizures greater than 30 minutes in duration, as compared to 4.8% during their original study baseline. The proportion of patients with DS with nonconvulsive seizures lasting longer than 30 minutes during the last 12 weeks of treatment was 4.8%, compared to 7.2% during their original study baseline.

Harms Results

A total of 306 patients with DS (97.1%) had 1 or more AE during the study, with 71 patients (22.5%) reporting AEs of mild severity, 157 patients (49.8%) reporting AEs of moderate severity, and 78 patients (24.8%) reporting severe AEs. SAEs were reported for 133 participants (42.2%) in the DS group, with the most common SAEs being status epilepticus, convulsion, and pneumonia. There were 28 patients (8.9%) with DS who stopped treatment due to AEs, with the most common AEs leading to discontinuation being convulsion, increased aspartate amino transferase, and increased alanine-amino transferase. A total of 6 patients (1.9%) with DS died during the study.

Critical Appraisal

The CARE5 study is a nonrandomized, open-label, single-arm study. The lack of comparison with an active comparator precludes the ability to assess the relative long-term therapeutic benefits or safety of cannabidiol versus other ASMs. Furthermore, the lack of blinding in the CARE5 study may affect subjective measures such as patient-reported outcomes. The direction and magnitude of this potential bias remain unclear.

Since completion of the CARE1 and CARE2 trials was an eligibility criterion for enrolment into the CARE5 trial, patients who discontinued the CARE1 and CARE2 studies for any reason, such as AEs, withdrawal by patient or parent, or withdrawal by investigator, were excluded from the CARE5 trial. Thus, enrolment into the CARE5 study was limited to those who tolerated and responded to cannabidiol. Moreover, only 54% of patients completed the study; as such, there is a risk of bias due to missing outcomes data. The proportion of patients who adhered to the study drug during the longer follow-up was not reported.

Indirect Comparisons

No indirect treatment comparisons were submitted by the sponsor.

Economic Evidence

Cost and Cost-Effectiveness

Table 5: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients aged 2 years and older with DS inadequately controlled by their current usual care (i.e., patients taking at least 1 ASM who experienced 4 or more convulsive seizures over a 28-day period)
Treatment	Cannabidiol plus usual care (assumed to be comprised of 1 or more ASMs[a])
Dose regimen	2.5 mg/kg twice daily (5 mg/kg/day) for 1 week, then increased to 5 mg/kg twice daily (10 mg/kg/day) to a maximum of 10 mg/kg twice daily (20 mg/kg/day) depending on individual response and tolerability
Submitted price	$1,424.54 per 100 mL bottle
Treatment cost	$5,200 to $83,193 per patient per year, depending on patient weight and dosage
Comparator	Usual care
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (90 years)
Key data sources	CARE1 and CARE2 clinical trials and the CARE5 extension study
Key limitations	• The full Health Canada indicated population for DS was not modelled. Effectiveness of cannabidiol plus usual care was based on observations from the CARE1 and CARE2 trials, which enrolled patients with 4 or more convulsive seizures per 28 days. The cost-effectiveness of cannabidiol among patients with fewer than 4 convulsive seizures per 28 days is unknown. • The efficacy of cannabidiol in the sponsor's model was based on observations from studies enrolling patients aged 2 to 18 years. As the severity and frequency of seizures differs between children and adults with DS, it is uncertain whether the magnitude of benefit associated with cannabidiol compared to usual care will be equivalent in adults. The incremental QALYs predicted with the use of cannabidiol plus usual care are thus uncertain. • The model structure, based on roughly dividing patients into 3 equal groups based on convulsive seizure

Component	Description
	frequency and number of seizure-free days per 28 days at baseline from the CARE1 and CARE2 studies, does not adequately reflect DS in clinical practice and does not represent homogeneous health states. • The sponsor's model predicts a gain in QALYs for 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 CARE5 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 onward (i.e., from approximately 2.5 years on treatment until death or discontinuation). As the CARE5 extension study enrolled patients who had completed the pivotal RCTs (CARE1 or CARE2), it is possible that the CARE5 extension study represents an enriched population of patients who were benefiting from cannabidiol in the RCTs. More than 99% of the incremental benefit associated with cannabidiol was accrued after the pivotal trials on the basis of data from the CARE5 trial and extrapolation. • The acquisition costs of cannabidiol were likely underestimated, as the sponsor's model 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 reflects patients from the CARE1 and CARE2 trials who were randomized to receive either 10 mg/kg/day or 20 mg/kg/day, and from the CARE5 extension study who had a mean dose of 22.18 mg/kg/day. Additionally, the body weights of patients may be underestimated given the approach taken by the sponsor. • The health state utility values adopted by the sponsor for patients with DS are highly uncertain and may not reflect the preferences of those living in Canada. The majority of incremental QALYs gained with cannabidiol plus usual care were accrued by caregivers, not patients with DS. • No uncertainty was incorporated for transitions between health states, which is inappropriate because it does not consider variability in treatment response. Transitions between health states that were not observed in the CARE1, CARE2, and CARE5 studies were assumed by the sponsor to be impossible, which lacks face validity. • The impact of AEs was not adequately considered, owing to the assumption that all SAEs have the same impact on HRQoL, the use of different incidence thresholds for cannabidiol plus usual care vs. usual care alone, and the lack of consideration of AEs experienced by patients who received 20 mg/kg/day in the CARE1 and CARE2 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 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 and beyond would continue at the rates used for cycles 2 to 9. CADTH was unable to address the remaining limitations. • The results of the CADTH base case suggest that cannabidiol plus usual care is more costly (incremental costs = $136,593) and more effective (incremental QALYs = 1.07) than usual care alone, resulting in an ICER of $128,062 per QALY gained. A price reduction of 44% for cannabidiol would be required for cannabidiol plus usual care to be cost-effective compared to usual care alone at a willingness-to-pay threshold of $50,000 per QALY gained.

AE = adverse event; ASM = antiseizure medication; DS = Dravet syndrome; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; RCT = randomized controlled trial; SAE = serious adverse event; vs. = versus.

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

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 DS, as only patients with drug-refractory DS were considered eligible for cannabidiol by the sponsor.
- The number of patients with DS in Canada is uncertain.
- The Non-Insured Health Benefits population was inappropriately calculated.
- The proportion of patients eligible for public drug plan coverage is uncertain and may be underestimated.
- Cannabidiol drug costs are uncertain and likely underestimated.
- The uptake of cannabidiol among patients with DS is uncertain and may be underestimated.

CADTH reanalyses aligned the eligible population with the Health Canada indication for DS, 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 DS is expected to be $937,992 in year 1, $1,986,853 in year 2, and $2,607,754 in year 3, for a 3-year total of $5,532,598. If reimbursement of cannabidiol is restricted to patients with drug-refractory DS, the 3-year budget impact of reimbursing cannabidiol is expected to be $4,979,339. The estimated budget impact is highly sensitive to the prevalence of DS and the uptake of cannabidiol.

CDEC Information

Members of the Committee

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

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Conflicts of interest: None

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