Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Cannabidiol (Epidiolex)

Indication: Use as adjunctive therapy for the treatment of seizures associated with Dravet Syndrome (DS) in patients 2 years of age and older.

Sponsor: Jazz Pharmaceuticals Canada Inc.

Recommendation: Reimburse with Conditions

Version: 1.0
Publication Date: March 2024
Report Length: 23 Pages

Single Technology

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

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

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that cannabidiol be reimbursed for the adjunctive therapy of seizures associated with Dravet Syndrome (DS) in patients 2 years of age and 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 one background antiseizure medication (median 3), resulted in added clinical benefit for patients aged between 2 and 18 years old who have seizures associated with DS. The CARE1B and CARE 2 studies demonstrated that, compared with placebo, 14 weeks of treatment with cannabidiol was associated with clinically meaningful reduction in the frequency of total seizures (convulsive and non-convulsive), higher proportion of patients reaching seizure control (defined as more than 50% reduction from baseline in seizure frequency), and an increase in seizure-free days. In CARE1B, patients in the 20 mg/kg/day cannabidiol group achieved a greater percentage reduction from baseline in convulsive seizure frequency than placebo (-38.9% vs, -13.3%, respectively). The estimated median difference between treatment arms was -22.8% (95% CI: -41.1, -5.4; p = 0.0123). Similar results were reported in CARE2, with reductions in convulsive seizures from 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, 3.7; p = 0.105) for cannabidiol 10 mg/kg/day and -19.9% (95%CI -33.9, 5.3; p = 0.008) for cannabidiol 20 mg/kg/day. In the CARE1B trial, the proportion of patients who achieved >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% vs 27.1%, respectively; p = 0.078). In the CARE2 trial, compared with placebo, the proportion of patients who achieved >50% reduction in seizure frequency was greater with either the 10 mg/kg/day cannabidiol doses (43.9% vs 26.2%, p = 0.033) or the 20 mg/kg/day cannabidiol doses (49.3% vs 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 treatment with cannabidiol compared with placebo.

Patients identified an unmet need for treatments that improve seizure control and health-related quality of life (HRQoL), increase the number of seizure-free days, decrease visits to healthcare facilities and the need for rescue medications, and decrease seizure burden without affecting mood, cognition, or their behaviour. Although there was insufficient evidence to evaluate the effects of cannabidiol HRQoL, CDEC concluded that the available evidence indicated that cannabidiol, as adjunctive therapy, met some patients-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 (ICER) for cannabidiol in combination with usual care was $128,062 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 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. Patients 2 years old or older, with at least 4 convulsive seizures per month. 1.2. Patients whose seizures are not adequately controlled with 2 or more other anti-seizure medications at the time of initiation.	Evidence from CARE1B and CARE2 pivotal trials demonstrated that treatment with cannabidiol resulted in seizure control benefits in DS patients 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 one 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 treatment, severe toxicity, or treatment intolerance.	Based on information from the pivotal trials and supported by input from the clinical experts.	—
Prescribing		
4. Cannabidiol for DS should be prescribed by neurologists or pediatric neurologists with experience in the treatment of patients with DS.	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 safety or potential clinical benefits of the cannabidiol preparation under review in patients who were using other cannabidiol products,	
Pricing		
6. A reduction in price	The ICER for cannabidiol plus usual care is $128,062 when compared with usual care alone.	—

Reimbursement condition	Reason	Implementation guidance
	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.	

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

Discussion Points

- A 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 MIDs were not identified for these outcomes, the assessment suggests that the results are likely to be clinically meaningful to patients. GRADE assessments rated as low certainty the evidence supporting other patients-identified relevant outcomes in the trials, such as HRQoL and sleep disruption, 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 in 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 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 adult patients, 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

Dravet syndrome (DS) is a very rare form of epilepsy associated with treatment-resistant, lifelong seizures and substantial comorbidities such as intellectual disability, behavioral, 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 previously developmentally normal infants. Approximately 70% to 85% of cases with clinical features of DS have mutations of the SCN1A gene. The estimated incidence of DS is one in 33 000 live births worldwide with a prevalence estimated at one in 45,700 children less than 18 years of age. In Canada the estimated prevalence is 1 in 40,000.

The 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 includes valproic acid and clobazam initially, but these are usually insufficient to control seizures. In patients who are refractory to initial therapies, clinicians may add other anti-seizure medications (ASMs) including stiripentol, topiramate, levetiracetam, clonazepam, and rufinamide. Cannabidiol is also recommended as an adjunctive treatment option for patients who fail 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), solution 100 mg/ml, oral, in the treatment of patients two years of age and older with seizures associated with DS.

Cannabidiol has been approved by Health Canada for the treatment of seizures associated with Dravet Syndrome (DS) in patients 2 years of age and older. Cannabidiol is a plant-derived pharmaceutical formulation available as 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 2 to 18 years of age with DS not completely controlled with current anti-epileptic medications.
- patients' perspectives gathered by one 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 Dravet Syndrome.
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

CADTH received input from the Canadian Epilepsy Alliance (CEA). CEA 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.

CEA highlighted that individuals with uncontrolled epilepsy are at risk of social isolation and mental illness. The unpredictable nature of seizure and side effects of medications have negative effects such as anxiety, depression, mood swings, sexual dysfunction, suicidal thoughts, and exhaustion on both 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 under-employed with restricted income and without access to employer-funded insurance plans, which limit their access to the 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 treatment goals of any therapy for patients with DS include improving seizure control with the improvement of health-related quality of life (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 healthcare facilities and the need for rescue medications. The clinical experts mentioned that cannabidiol has the potential of fewer adverse effects when compared to other drugs indicated for this condition. Initially, it was anticipated that cannabidiol will be used after valproic acid and clobazam. The experts mentioned that cannabidiol may be useful in the treatment paradigm in adult patients 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 frequency and 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 endpoints when assessing response to treatment. Experts mention that they would consider the inadequate improvement in seizure frequency (approximately less than 50% in change from baseline) and intolerable adverse events 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 be the ones monitoring 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 (if applicable)
Relevant comparators	
The manufacturer 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 HC indication for DS. In CARE1 and CARE2, 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 two drugs.	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.

Drug program implementation questions	Response from clinical experts and presenters (if applicable)
British Columbia reimbursement criteria also require documented inadequate response to levetiracetam or topiramate.	
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 resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used anti-epileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom." Inclusion criteria for CARE1 and CARE2 included patients on 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 who are refractory to initial therapies can attempt to add-on ASMs including: stiripentol, topiramate, levetiracetam, clonazepam, and rufinamide. Cannabidiol is also recommended as an adjunctive treatment option for patients who fail first line ASMs. The HC indication/reimbursement criteria for stiripentol include combination treatment with both valproate and clobazam. Question for CDEC and Clinical Expert: *Would it be appropriate to require patients to be on both valproate and clobazam prior to 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 and requiring two specific treatments will not be needed. CDEC agreed with the clinical experts that specifying two medications is not required. However, CDEC added the reimbursement condition requiring patients to have inadequate seizure control on at least two other anti-seizure medications at the time of initiation with cannabidiol.
Considerations for continuation or renewal of therapy	
Uncontrolled patients with DS typically experience dozens of convulsive seizures each month. Treatment goals focus on balancing optimal seizure control - reducing 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 endpoint in the CARE1 and CARE2 trials was the percent change from baseline in convulsive seizure frequency. *Question for CDEC and clinical expert: 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 room 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 presentation of seizure episodes (from one per week to hundreds per day), and the value patients and caregivers may have in defining a meaningful benefit or lack thereof (see discontinuation below).
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	

Drug program implementation questions	Response from clinical experts and presenters (if applicable)
Question for clinical experts and CDEC: 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 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	
Question for the clinical expert: 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 within 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 prescription criteria of cannabidiol should be like that of stiripentol and 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). They were excluded from the CARE1 and CARE2 trials.	*This was a comment from the drug programs to inform CDEC deliberations.*
Patients with other forms of treatment-resistant epilepsy, who fall outside the HC 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
• List price of Cannabidiol (cannabidiol) 100mg/ml oral solution is $1,424 per 100 ml bottle.
• According to the manufacturer's BIA:
  ○ The average annual cost for maintenance dosing at 10mg/kg/day is $16K (pediatric patient) and $25K (adult patient). (*Would be double the cost at a maximum dose of 20mg/kg/day.)*
  ○ 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.
	This was a comment from the drug programs to inform CDEC deliberations.

Drug program implementation questions	Response from clinical experts and presenters (if applicable)
○ The incremental budget impact is $559K in Year 1, $1.1M in Year 2, $1.5M in Year 3, for a cumulative three-year budget impact of $3.2M.	
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 = anti-seizure medications; AST = aspartate amino transferase; BIA = budget impact analysis; CDEC = Canadian Drug Expert Committee; DS = Dravet Syndrome; HC = Health Canada.

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 3, 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 2 to 18 years of age 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 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 2 to 18 years of age and were receiving multiple therapies for controlling their seizures. The 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 CARE1 Part B, 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, -4.8) versus -13.3% (95% CI: -52.5, 20.2) for the placebo group. The estimated median difference between treatment arms was -22.8% (95% CI: -41.1, -5.4; p=0.0123).

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

Proportion of patients with a ≥50% reduction in convulsive seizure frequency from baseline during the treatment period

In CARE1 Part B, 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, 0.323) in favour of the intervention. There were twice the odds of achieving this endpoint in the cannabidiol group compared to placebo (OR: 2.00; 95% CI: 0.93, 4.30) (p=0.0784).

In CARE2, 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, with 29 of 66 patients (43.9%) and 20 mg/kg/day with 33 of 67 patients (49.3%) groups when compared to placebo, with 17 of 65 patients (26.2%). The difference in proportion was of 0.178 (95% CI: 0.017, 0.338) in the 10 mg/kg/day group vs placebo and of 0.231 (0.071, 0.391) in the 20 mg/kg/day vs placebo. The odds of achieving this endpoint were higher in both the 10 mg/kg/day group (OR: 2.21; 95% CI: 1.06, 4.62) (p=0.0332) and the 20 mg/kg/day group (2.74; 95% CI: 1.32, 5.70) (p=0.0069) when compared to placebo.

Proportion of patients with a ≥75% reduction in convulsive seizure frequency from baseline during the treatment period

In CARE1 Part B, 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 compared to placebo, with 14 of 61 patients (23%) and 7 of 59 (11.9%) patients respectively. The difference in proportions (95% CI) was of 0.111 (-0.023, 0.245) in favour of the intervention. The odds of achieving a 75% or greater reduction was 2.21 (95% CI: 0.82, 5.95) (p=0.1121) in favour of the 20 mg/kg/day group.

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

Number of convulsive seizure free days

In CARE2, the mean number of convulsive seizure free days increased in all three 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 with a treatment difference of 2.4 (95% CI: 1.0, 3.9) (p=0.0009) between the 10 mg/kg/day group and placebo, and 1.3 (95% CI: -0.1, 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 CARE1 Part B, 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, -4.0) compared to the placebo group (-9.0; 95% CI: -51.4, 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 CARE2, the percentage reduction was 56.4 (95% CI: 47.8, 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, 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 CARE1 part B, there was only one case (1.6%) in the 20 mg/kg/day group vs 0 in the placebo group at the end of the treatment period. Similarly, patients in the CARE2 study presented status epilepticus in numbers 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 CARE1 Part B and CARE2 had a poor quality of life based on the low mean overall 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 CARE1 Part B with an adjusted mean difference (95%CI) of 1.5 (−3.8, 6.8; p=0.576), and 3.8 (−0.1, 7.8; p=0.058) and 1.8 (−2.2, 5.8; p=0.382) points of the score in the 10 mg/kg/day and 20 mg/kg/day doses in CARE2 respectively over placebo.

Sleep Disruption and Function

In both CARE1 Part B and CARE2, mean baseline sleep disruption numerical rating scale (NRS) scores were similar across the treatment groups. In CARE1 Part B, a mean treatment difference in sleep disruption score of -0.4 (95% CI: -1.5, 0.7) was observed, with no evidence of a significant difference between cannabidiol 20 mg/kg/day and placebo. Similarly, in CARE2, the mean treatment difference in sleep disruption score between the 10 mg/kg/day cannabidiol group and placebo was 0.0 (95% CI: -0.9, 0.8) and between the 20 mg/kg/day cannabidiol and placebo was -0.1 (95% CI: -0.9, 0.8).

When evaluating the mean Epworth sleep scale (ESS) scores at baseline, these were relatively high in both trials in all treatment groups (>7.1 in CARE1 Part B, >7.2 in CARE2). In CARE1 Part B, the mean treatment difference in ESS score between the 20 mg/kg/day Cannabidiol group and placebo was 1.51 (95% CI: -0.18, 3.19) in favour of placebo (p=0.078). In CARE2, the mean

treatment difference in ESS score between the 10 mg/kg/day group and placebo was -0.55 (95% CI: -1.86, 0.75) (p=0.404) and 0.74 (95% CI: -0.57, 2.05) (p=0.267) between the 20 mg/kg/day group and placebo.

Resource use

In CARE1 Part B, a total of six patients (5%) reported one or more inpatient hospitalizations due to epilepsy during the treatment period: five patients (8.2%) in the 20 mg/kg/day cannabidiol group and one patient (1.7%) in the placebo group. In CARE2, a total of 26 patients (13.1%) reported one or more inpatient hospitalizations due to epilepsy: eight patients (11.9%) in the 20 mg/kg/day cannabidiol group, 12 patients (18.2%) in the 10 mg/kg/day cannabidiol group, and six 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, 36 patients (59.0%) and 41 (69.5%) in the cannabidiol 20 mg/kg/day and placebo group respectively used rescue medication, while in the CARE2 study the numbers 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 CARE1 Part B, 57 of 61 (93.4%) patients in the 20 mg/kg/day cannabidiol group and 44 of 59 (74.6%) patients in the placebo group reported one or more adverse events (AE). In CARE2, 56 of 64 (87.5%) patients in the 10 mg/kg/day cannabidiol group, 62 of 69 (89.9%) patients in the 20 mg/kg/day cannabidiol group, and 58 of 65 (89.2%) patients in the placebo group reported one 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 CARE1 Part B, 10 of 61 (16.4%) patients in the 20 mg/kg/day cannabidiol group and 3 of 59 (5.1%) patients in the placebo group reported one or more serious adverse events (SAE). In CARE2, 13 of 64 (20.3%) patients in the 10 mg/kg/day cannabidiol group, 17 of 69 (24.6%) patients in the 20 mg/kg/day cannabidiol group, and 10 of 65 (15.4%) patients in the placebo group reported one 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 CARE2. All SAEs were resolved in the CARE1 Part B study, while three patients in the 20 mg/kg/day cannabidiol group in CARE2 had three 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 CARE1 Part B, AEs that led to discontinuation of the medication occurred in 9 of 61 (14.8%) patients of 20 mg/kg/day cannabidiol group and in 1 of 59 (1.7%) of placebo patients, while in CARE2, 5 of 69 (7.2%) patients in the 20 mg/kg/day cannabidiol group experienced AEs leading to discontinuation from the study. No patients in the 10 mg/kg/day cannabidiol group or placebo groups withdrew from the study due to AEs. No patient deaths occurred during either study.

Critical Appraisal

Both 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 low risk for introducing bias. There was good adherence to the intended interventions. There were, however, some imbalances observed in the use different co-interventions; although these possible deviations could introduce bias, the impact and direction of the bias on the outcomes of interest is uncertain. Some modifying effects from variables were observed (i.e., use of stiripentol, use of clobazam, and geographical location); however, the low 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 outcome data. In both studies, measurements of the outcomes were appropriate. The blinding of participants and clinical investigators kept throughout the conduction of the studies mitigates potential biases in this domain. Overall, both studies demonstrate 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 endpoints depicting statistically significant results lacked multiplicity control carrying a risk of false positives, hence cautious interpretation due to potential 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 above 18 years of age since no patients above this age 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 on whether the results can be generalized to patients with less than 4 seizures per month since 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, the clinical experts suggested that this is an important consideration, but it is unlikely to affect the generalizability of the results of the studies.

The question if 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 varies and makes it difficult to assess this question using indirect comparison since 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 was 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 (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Cannabidiol 10 mg/kg/day	Difference		
Seizure Control							
Median % change from baseline of convulsive seizures frequency Follow-up: 14 weeks	131 (1 RCT)	NA	-24.5%	-41.2% (95% CI -81.0, 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 (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 (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 in total seizures frequency change from baseline. Follow up: 14 weeks	131 (1 RCT)	NA	The change from baseline in the intervention group was -51.9% (95% CI: -79.3 to -14.5) while in the placebo group 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	The number of patients with status epilepticus went from 4 of 66 (6.1%) at baseline to 3 (4.5%) at end of treatment in the intervention group, while in the 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.
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 the HRQoL when compared to placebo. The clinical meaningfulness of the results is uncertain.
Sleep Disruption							
Change from baseline in mean ESS and 0-10 NRS scores Follow-up: 14 weeks	131 (1 RCT)	NA	The mean difference in the Sleep Disruption 0-10 NRS scale was 0 (95% CI -0.9, 0.8), while the mean difference in the ESS score was -0.55 (-1.86, 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							

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Cannabidiol 10 mg/kg/day	Difference		
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; meanwhile, 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	The number (%) of patients experiencing AEs in the cannabidiol 10 mg/kg/day and placebo groups were, respectively 56 (87.5%) vs 58 (89.2%), SAEs 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

a. Rated down for imprecision one level. The target of our certainty is on a non-trivial 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 1000 treated as considered by clinical experts consulted by CADTH.

c. Rated down two 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 for imprecision two levels. Based on the target of the certainty of a meaningful effect of the intervention, the 95%CI was considered wide and no threshold of an MID could be obtained.

e. Rated down for imprecision. No CIs could be assessed. Rated down due to small sample size which 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 (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Cannabidiol 20 mg/kg/day	Difference		
Seizure Control							
Median % 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 (0.93 to 4.30) Care 2: OR 2.74 (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 (0.82 to 5.95) Care 2: OR 3.33 (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.
Median % 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% (-67.1, -13.1) while in the placebo group was -26.8% (-58.1, 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.
% patients with convulsive status epilepticus, change from baseline Follow up: 14 weeks	252 (2 RCTs)	NA	• **CARE1b study**: The number of patients went from 0/61 at baseline to 1 (1.6%) at end of treatment in the intervention group, while in the placebo group went from 1/59 (1.7%) to 0 patients. • **CARE2 study**: The number of patients went from 6 of 67 (9%) at baseline to 9 (13.4%) at end of treatment in			Low [d]	Cannabidiol 20 mg/kg/day may produce little to no difference in the frequency of status epilepticus from baseline compared to placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Cannabidiol 20 mg/kg/day	Difference		
			the intervention group, while in the placebo group went from 4 of 65 (6.2%) to 8 (12.3%).				
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 0-10 NRS Follow-up: 14 weeks	252 (2 RCTs)	NA	• **CARE1b study**: The mean difference (95%CI) in the Sleep Disruption 0-10 NRS scale was -0.4 (-1.5, 0.7), while the mean difference in the ESS score was 1.51 (-0.18, 3.19). • **CARE2 study**: The mean difference (95%CI) in the Sleep Disruption 0-10 NRS scale was -0.1 (95% CI -0.9, 0.8), while the mean difference in the ESS score was 0.74 (-0.57, 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.
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 due to 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 one 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 respectively, SAEs in 17 (24.6%) vs 10 (15.4%), liver			Low [d]	Cannabidiol 20 mg/kg/day may produce more AEs and SAEs as well as cases of somnolence and investigations of liver enzymes than placebo. The clinical meaningfulness of these results is uncertain.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Cannabidiol 20 mg/kg/day	Difference		
			enzyme investigations 3 and 0, somnolence in 2 and 0 patients respectively.				

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

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 1000 treated as considered by the clinical experts consulted by CADTH
b. Rated down -1 for imprecision. The target of the certainty is that of any beneficial effect (based on the null). Only one 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 which 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 two 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 an MID could be obtained. Sample size was considered low in relation to a plausible OIS.
Source: These results were obtained from the CARE1 part B and CARE 2 studies.

Long-Term Extension Studies

Description of Studies

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

Efficacy Results

During weeks 37-48 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% reduction in total seizure frequency during weeks 37-48 of treatment was 59.3%. Out of all patients with DS, 70.1% experienced a ≥25% reduction in total seizure frequency, 39.7% experienced a ≥75% reduction in total seizure frequency, and 6.1% experienced total seizure freedom (100% reduction).

During weeks 37-48 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% reduction in convulsive seizure frequency during weeks 37-48 of treatment was 52.3%. Out of all patients with DS, 67.8% experienced a ≥25% reduction in convulsive seizure frequency, 34.6% experienced a ≥75% 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 non-convulsive seizures greater than 30 minutes in duration 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 one or more AEs during the study, with 71 (22.5%) patients reporting AEs of mild severity, 157 (49.8%) patients reporting AEs of moderate severity, and 78 (24.8%) patients reporting severe AEs. SAEs were reported for 133 (42.2%) participants in the DS group, with the most common SAEs being status epilepticus, convulsion, and pneumonia. There were 28 (8.9%) patients with DS who stopped treatment due to AEs, with the most common AEs leading to discontinuation being convulsion, increased AST, and increased ALT. A total of 6 (1.9%) patients with DS died during the study.

Critical Appraisal

The CARE5 study is a non-randomized, 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 antiseizure medications. Furthermore, the lack of blinding in CARE5 may affect subjective measures such as patient reported outcomes. The direction and magnitude of this potential bias remains unclear.

Since completion of CARE1 and CARE2 was an eligibility criterion for enrollment into CARE5, patients who discontinued CARE1 and CARE2 for any reason such as adverse events, withdrawal by patient/parent, or withdrawal by investigator; were excluded from CARE5. Thus, enrollment intoCARE5 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 ITCs 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 two years and older with DS inadequately controlled by their current usual care (i.e., patients taking at least one anti-seizure medication [ASM] who experienced four more convulsive seizures 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)
Key data sources	CARE1 and CARE2 clinical trials, 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. • 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 three equal groups based on convulsive seizure frequency and number of seizure free days per 28-days at baseline from the CARE1 and CARE2, 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 CARE5 enrolled patients who had completed the pivotal RCTs (CARE1 or CARE2), it is possible that CARE5 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 CARE5 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

Component	Description
	model reflects patients from the CARE1 and CARE2 trials who were randomized to receive either 10 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 weight 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 CARE1, CARE2, and CARE5 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 versus 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 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: $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.

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

[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 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.
- The uptake of cannabidiol is 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 three-year total of $5,532,598. If the reimbursement of cannabidiol is

restricted to patients with drug-refractory DS, the three-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.

Meeting date: February 29, 2024

Regrets:

None

Conflicts of interest:

None