Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Cannabidiol (Epidiolex)

Indication: As adjunctive therapy for the treatment of seizures associated with Tuberous Sclerosis Complex (TSC) 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: 24 Pages

Single Technology

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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 as adjunctive therapy for the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients 2 years of age and older, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Tuberous sclerosis complex is a rare, multisystem disorder where seizures of varying types are the most common neurological manifestation of the disease, affecting up to 70% of patients. TSC-associated seizures generally begin during the first year of life, progressing aggressively over time, resulting in substantial disease-related morbidity and potential early mortality.

One phase III, double-blind randomized controlled trial (RCT) (CARE6; N = 224) demonstrated that in patients with TSC-associated epilepsy that was not completely controlled by their current anti-seizure medication (ASM), treatment with cannabidiol resulted in added clinical benefit compared with placebo, based on the change from baseline in TSC-associated seizure frequency. In the CARE6 trial, the mean change from baseline in TSC-associated seizures was 48.6% for patients who received cannabidiol 25 mg/kg/day and 26.5% for patients who received placebo. This was associated with a mean percent reduction in seizure frequency from baseline at 16 weeks of 31.0% (95% CI, 13.9 to 43.3; p = 0.0009), in favour of cannabidiol. In addition, the proportion of patients with a reduction in seizure frequency of 50% or more was 36.0% among patients receiving cannabidiol and 22.4% for placebo (OR = 1.95, 95% CI, 0.95 to 4.00). In clinical practice, 20% to 30% of patients with seizures associated with TSC are expected to have a strong response to treatment (i.e., 50% reduction), which was demonstrated in the cannabidiol treatment group.

Patients identified a need for new, effective therapies that reduce seizure frequency and severity, which ultimately impact overall quality of life (QoL). Additionally, treatments that are associated with fewer side effects were desirable to patients. Based on the evidence reviewed, CDEC concluded that cannabidiol may meet some of these needs including the reduction in seizure frequency, however, there was insufficient evidence to evaluate the effect of cannabidiol on seizure severity, total seizure freedom, and HRQoL and cognition.

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 $295,503 per quality-adjusted life-year (QALY) compared with usual care alone. At this ICER, cannabidiol is not cost-effective at a $50,000 per QALY gained willingness to pay (WTP) threshold for patients 2 years of age and older with TSC and a history of epilepsy that is inadequately controlled by their current anti-seizure medication (ASM). A price reduction is required for cannabidiol to be considered cost-effective at a $50,000 per QALY gained threshold.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with cannabidiol should be reimbursed in patients with a confirmed diagnosis of seizures associated with TSC who meet the following criteria: 1.1. 2 years of age or older 1.2. Currently taking 1 or more ASMs at stable doses for at least 4 weeks prior to initiation	Evidence from the CARE6 trial demonstrated a clinical benefit in the enrolled population which included patients with a clinical diagnosis of TSC according to the criteria agreed by the 2012 International Tuberous Sclerosis Complex Consensus Conference who were receiving 1 or more ASMs at a dose which had been stable for at least 4 weeks prior to screening.	Clinicians follow the updated 2021 International Tuberous Sclerosis Complex Consensus guidelines when diagnosing TSC. The updated guidance is considered appropriate to identify patients with TSC despite the CARE6 trial enrolling patients based on the 2012 guidelines.
2. Patients must have the following: 2.1. At least 8 seizures per 28 days prior to initiation of cannabidiol. 2.2. Inadequately controlled seizures despite previously or currently receiving treatment with at least 2 ASMs.	In the CARE6 trial, patients had to have experienced at least 8 seizures during the first 28 days of the baseline period, with at least 1 seizure occurring in at least 3 of the 4 weeks. In the baseline period, patients experienced 8 to 558 TSC-associated seizures. There is no evidence to support the use of cannabidiol in patients with less than 8 seizures per 28 days. Patients in the CARE6 trial receiving a median of 4 prior, and 3 concurrent ASMs at baseline. The clinical experts suggested prior treatment with at least 2 ASMs, which is aligned with the definition of refractory seizures commonly used in current clinical practice.	The Task Force of the ILAE Commission on Therapeutic Strategies proposed that drug resistant epilepsy be defined as "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom"[a]
Renewal		
3. The maximum duration of initial authorization is 6 months. For renewal after initial authorization, the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement.	The clinical experts noted that patients with TSC-associated seizures, would ideally be seen as often as every 3 months to monitor treatment and perform any medication adjustments, though in practice, most are mostly seen every 6 months. As such, it is appropriate to require an assessment of response to treatment at least every 6 months.	—
Discontinuation		
4. Treatment with cannabidiol should be discontinued due to lack of beneficial clinical effect, severe toxicity, or treatment intolerance.	To ensure that cannabidiol is being used safely in patients who are benefiting from treatment.	—
Prescribing		
5. The patient must be under the care of a neurologist with experience in	Accurate diagnosis and management of patients with TSC-associated seizures is important to ensure that cannabidiol is	—

Reimbursement condition	Reason	Implementation guidance
the diagnosis and management of TSC.	prescribed to appropriate patients and that severe adverse effects are managed in an optimized and timely manner.	
6. Cannabidiol should not be reimbursed when given in the following instances: 6.1. In patients concurrently using mTOR inhibitors 6.2. In patients concurrently using recreational or medicinal cannabis or other cannabinoid-based medications.	There is no evidence to support the use of cannabidiol in conjunction with mTOR inhibitors, or in patients who use recreational or medicinal cannabis. Patients taking oral mTOR inhibitors, and patients who use or have in the past used recreational or medicinal cannabis, or cannabinoid-based medications within the 3 months prior to screening or had a known or suspected history of substance abuse were excluded from the CARE6 trial.	—
Pricing		
7. A reduction in price	The ICER for cannabidiol in combination with usual care is $295,503 per QALY gained when compared with usual care alone. A price reduction of at least 63% would be required for cannabidiol in combination with usual care to achieve an ICER of $50,000 per QALY gained compared to usual care alone.	—
Feasibility of adoption		
8. The feasibility of adoption of cannabidiol must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.	—

ASM = anti-seizure medication; CI = confidence interval; mTOR = mammalian target of rapamycin; TSC = tuberous sclerosis complex.

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

Discussion Points

- TSC is a rare, heterogeneous disease that results in debilitating neurological condition characterized by seizures and neuropsychiatric disorders (i.e., TANDs) such as mental retardation and behavioral disorders. CDEC acknowledged the importance of reducing seizure frequency on overall QoL, though despite many currently available ASMs, patients continue to suffer from severe and debilitating seizures. CDEC discussed the unmet therapeutic need and substantial disease-related morbidity in TSC-associated epilepsy and noted that cannabidiol may provide an additional treatment option to reduce seizure burden.
- The patients enrolled in CARE6 experienced at least 8 seizures per 28-day period (median, 56.93 [range, 8 to 558.0]), and previously received a median of 4 (range, 0 to 15) prior ASMS and were currently receiving a median of 3 (range, 0 to 5) concurrent ASMs. In discussion with the clinical experts, CDEC noted that the population included in the CARE6 trial were heavily pre-treated and had refractory disease with a high seizure burden. CDEC concluded that the benefit for patients with less than 8 TSC-associated seizures per 28 days remains unknown.
- CDEC considered the evidence from the phase III CARE6 trial which demonstrated that cannabidiol 25 mg/kg/day resulted in a statistically significant reduction in TSC-associated seizure frequency compared to placebo (31.0% [95% CI, 13.9 to 43.3]). Since the 95% CI of the primary endpoint contained the potential for no clinical benefit, and the estimated absolute placebo-adjusted reduction (22.1% [95% CI, Not Reported]) was below the threshold of 25%, CDEC considered the magnitude of clinical benefit to be uncertain. Of note, results for outcomes related to seizure frequency were associated with a moderate level of certainty per the GRADE assessment due to imprecision and uncertainty in the magnitude of effect of cannabidiol. CDEC also discussed the definition of a clinically meaningful reduction in seizure frequency based on the CARE6 trial (e.g. a 25%, 50%, or 75% reduction in seizure frequency). Although this is often defined as a 50% reduction in seizure frequency in clinical trials, CDEC acknowledged that there is heterogeneity in the frequency and type of seizures among patients with TSC and by extension, variation in the definition of a clinically meaningful improvement in clinical practice. As a result, it is considered appropriate to define a clinically meaningful improvement based on clinical expertise.
- For the key secondary endpoint of proportion of patients achieving a 50% reduction in TSC-associated seizures, the results were considered clinically meaningful, however, they were not statistically significantly different from the placebo group due to the change from baseline observed for placebo (36.0% vs. 22.4%; mean difference, 13.6% [95% CI, -0.7 to 28.0]).
- CDEC discussed the overall uncertainty in the outcomes of seizure severity, seizure freedom, HRQoL, rescue medication use, and status epilepticus given their secondary and exploratory nature, as well as the limited availability of data. Complete seizure freedom was highlighted as an important outcome by patients and clinicians in improving QoL; however, the potential benefit of cannabidiol on seizure freedom remains unknown as only 1 patient in the cannabidiol group achieved complete seizure freedom in the CARE6 trial and the analyses were not included in the statistical testing hierarchy. Improvement in HRQoL and TAND were also outcomes identified as important to patients and caregivers, however, the impact of cannabidiol on these outcomes was unknown given the limited sample sizes and low completion rates for HRQoL measures, which the clinical experts noted were not used in clinical practice. Additionally, no outcomes related to behaviour or cognition were evaluated in the CARE6 trial. Moreover, CDEC considered the short duration of the CARE6 trial of 113 days insufficient to evaluate the impact of cannabidiol on HRQoL and TANDs.
- Only evidence from the cannabidiol 25 mg/kg/day group was evaluated by CDEC. Lower (10 mg/kg/day) and higher (50 mg/kg/day) dosages were not considered for TSC-associated seizures as these doses are not approved by Health Canada, though CDEC acknowledged the potential for differences in dosing.
- At the time of the CARE6 trial, patients receiving mTOR inhibitors (e.g., everolimus, sirolimus) were excluded given their changing regulatory approval status. CDEC discussed the anti-tumoral effect of mTOR inhibitors that may result in decreased seizure frequency or severity, and the challenge associated with determining the treatment benefit of cannabidiol if used concomitantly. Further, there is no evidence to support the concomitant use of cannabidiol and mTOR inhibitors in patients with TSC-associated seizures.
- The long-term efficacy and safety of cannabidiol cannot be established based on the results of the CARE6 trial. Results of the open-label extension trial were generally consistent with the double-blind phase of the CARE6 trial, however, CDEC noted that the limitations of the open-label extension study including the lack of comparator, and a population consisting of patients who completed the CARE6 double-blind period limited the interpretation and generalizability of the results.
- CADTH has concurrently reviewed cannabidiol for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome. The cost-effectiveness results of these evaluations may not be directly comparable, owing to differences in model structure, clinical effectiveness parameters, health state utility values, and cost inputs. The committee noted the high degree of uncertainty within the economic evaluation – notably, the lack of alignment between the model structure and

the expected clinician and patient experience of TSC and the limitations within the method of estimating utility – that could not be addressed through reanalysis. A greater price reduction may therefore be warranted.

Background

TSC is a rare genetic disorder resulting in the formation of benign tumours in many different organs, primarily in the brain, heart, lungs, kidneys, skin, and eyes. Though Canadian-specific estimates are lacking, TSC is estimated to occur in 1 out of 5,000 to 10,000 live births and has a prevalence of 8.8 cases per 100,000 people. Epileptic seizures of varying types are the most common neurological manifestation of the disease, affecting upwards of 70% of patients, and are also a significant cause of morbidity and mortality in patients with TSC. Uncontrolled epilepsy is among the most common causes of death in TSC, as a result of status epilepticus or Sudden Unexpected Death in Epilepsy (SUDEP). Clinically, the most effective prevention strategy for death related to epilepsy is to reduce the frequency of seizures.

Tuberous sclerosis complex-associated seizures generally begin within the first year of life in most patients (62.5% to 73.0%), beginning as infantile spasms, characterized by sudden and brief extension or flexion of the extremities. Other seizure types associated with TSC include focal seizures in about two-thirds of patients that can present with variable symptoms, which can evolve to a more generalized seizure, including tonic (brief tonic extension of the extremities, sometimes resulting in a fall), atonic (sudden loss of muscle tone resulting in a fall), or tonic-clonic (involving both stiffening and twitching or jerking of extremities) seizures, which become refractory in two-thirds of patients. Seizure burden in patients with TSC can be high, with untreated patients reporting an average of 87 TSC-associated seizures per month. Patients with TSC-associated seizures often have severe impairment of daily functioning or a history of epilepsy-related injuries. As a result, TSC-associated epilepsy has a severe impact on patients' QoL. Patients with TSC and early onset of seizures experience greater impairment in intellectual development than those without seizures and the early appearance of seizures usually results in severe forms of intellectual disability. Tuberous sclerosis complex is a chronic, life-long condition, and although the prognosis for many people living with TSC has improved over the years and life expectancy has increased, careful monitoring of all organ systems and development is critical, with most patients requiring multidisciplinary care at tertiary institutions as a result of their seizures and/or aspects of TSC-associated neuropsychiatric disorders (TAND).

Tuberous sclerosis complex may present at any age and is often diagnosed based on specific clinical criteria and/or genetic testing. Major clinical diagnostic criteria include: 3 or more hypomelanotic macules at least 5mm in diameter, 3 or more angiofibromas or fibrous cephalic plaques, 2 or more ungual fibromas, shagreen patch, multiple retinal hamartomas, multiple cortical tubers and/or radial migration lines, 2 or more subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis, and more than 2 angiomyolipomas. Minor diagnostic features of TSC include: "confetti" skin lesions, more than 3 dental enamel pits, more than 2 intraoral fibromas, retinal achromatic patch, multiple renal cysts, nonrenal hamartomas, and sclerotic bone lesions. Patients who have definite TSC have 2 major features or 1 major feature and 2 minor features. Possible TSC is considered in patients with either 1 major feature or 2 or more minor features. Two genes have been identified that can cause TSC: TSC1 and TSC2. Only one pathogenic variant in either of these genes is required for TSC to be present.

The goal of treatment in patients with TSC-related seizures is to prevent or control seizures, which may improve cognitive neurodevelopment and enhance HRQoL. There are limited options for disease-modifying medical therapies in TSC, and no Canadian guidelines exist for the management of TSC-related seizures. International guidelines broadly agree on the overall strategy with anti-epileptic drugs as the mainstay of current pharmacological treatment consisting of sodium valproate, vigabatrin, levetiracetam, clobazam, lamotrigine, lacosamide, oxcarbazepine, topiramate, and carbamazepine in Canada. Additional non-pharmacological treatment for seizures related to TSC include ketogenic diet, surgery for tumour removal, and vagus nerve stimulation (VNS).

Cannabidiol has been approved by Health Canada as adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or TSC in patients 2 years of age and older. The anti-seizure mechanism of Epidiolex is unknown, though it is structurally distinct from other ASMs. Cannabidiol reduces neuronal hyperexcitability through modulation of intracellular calcium via G protein-coupled receptor 55 and transient receptor potential vanilloid cation channel subfamily V member 1, and modulation of adenosine-mediated signaling through inhibition of adenosine transport via the equilibrative nucleoside transporter-1. It is available as an oral solution and the dosage recommended in the product monograph is 2.5 mg/kg taken twice daily (5 mg/kg/day). After one week, the dosage should be increased to 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, the dose can be further increased up to a maximum recommended dose of 12.5 mg/kg twice daily (25 mg/kg/day).

Sources of Information Used by the Committee

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

- A review of 1 phase III, placebo-controlled RCT in children and adults with TSC-associated seizures.
- Patients' perspectives gathered by patient groups, the Canadian Epilepsy Alliance (CEA), and Tuberous Sclerosis Canada Sclérose Tubéreuse (TSCST).
- Input from public drug plans and cancer agencies that participate in the CADTH review process.
- 2 clinical specialists with expertise diagnosing and treating patients with TSC-associated epilepsy.
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Two patient groups provided input for this review: the Canadian Epilepsy Alliance (CEA), and Tuberous Sclerosis Canada Sclérose Tubéreuse (TSCST). The CEA collected input from its 24 member associations on knowledge and experience of patients, caregivers, clinicians, volunteers, and supporters. The input from TSCST was gathered from a survey of 11 patient and caregiver members conducted in September 2023.

Both patient groups emphasized the catastrophic nature of uncontrolled seizures in infants and children, which are linked to cognitive delays, physical disabilities, and a high correlation of mental illness including depression and anxiety. Seizures occur so frequently that patients are unable to achieve milestones, learn, and even sleep. Patient groups note that seizures associated with TSC are typically hard to control and require constant monitoring and medication changes to try to get a combination that works to control, or at least reduce, the number of seizures. Patient groups noted that when someone has epilepsy, the whole family is affected, highlighting the tremendous burden of uncontrolled seizures on caregivers. Patients and caregivers experience anxiety around when and where the next seizure will occur, and what impact it will have. Caregivers are often sleep deprived and constantly fatigued due to sleep interruptions or anxiety. As well, caregivers are exposed to the sometimes highly unpleasant side effects including mood swings, sexual dysfunction, suicidal thoughts, memory loss, problems with concentration, fatigue, exhaustion, and depression, which are exacerbated by various medications.

Both patient groups emphasized the importance of total seizure freedom or reduction in seizure frequency in improving overall QoL. Patient groups cited that seizure control improves more than just developmental milestones, but day-to-day life as well, leading to fewer postictal side effects, better sleep, and less fatigue, confusion, anxiety, headaches, among others. Additionally, both patient groups highlighted the physical and emotional wellbeing of both caregivers and patients' ability to get an education or full-time employment, as well as the importance of social interactions in an otherwise isolating disease, which could all be improved by greater seizure control.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Given that TSC is a lifelong disease, the experts noted that the main goals of treatment include seizure reduction, and improved QoL, cognition, and behaviour, without side effects that worsen comorbidities. Other goals include prevention of SUDEP, reduction of caregiver burden, and greater independence for patients.

Current pharmacological treatment for TSC-associated seizures includes ASMs, which the experts noted are generally directed at the specific types of seizure and is often age related. The experts highlighted that most patients present with infantile spasms, which are generally treated with first line vigabatrin followed by corticosteroids. Focal seizures are often treated with sodium channel blockers (e.g., carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, phenytoin), whereas generalized seizures are often treated with broad-spectrum agents (e.g., valproate, clobazam, lamotrigine, topiramate, levetiracetam, brivaracetam). Treatments targeting the mTOR pathway such as everolimus and sirolumus are used to treat some of the tumors associated with TSC, however,

there is controversy about whether they improve seizure frequency and neuropsychiatric comorbidities. Additionally, mTOR inhibitors require chronic use and have potential serious side effects that require close monitoring. Interruption of the use of mTOR inhibitors can lead to tumor regrowth or seizure worsening, and the long-term effects of mTOR inhibition on TSC are still uncertain. Despite many currently available ASMs, response is highly variable, and patients continue to suffer from severe and debilitating seizures. The clinical experts highlighted that cannabidiol does not address the underlying disease process any more than other conventional ASMs, however, the distinct mechanism of action of cannabidiol could be complementary to other ASMs. Current treatments are often associated with side effects including sedation, or liver toxicity that can worsen comorbidities such as those related to behavior and may require constant monitoring.

The clinical experts noted that patients with TSC-associated seizures most in need of intervention would be those whose seizures remain uncontrolled by their current therapies, or in patients with behavioural issues with their current treatments. The experts considered patients who most likely to benefit from cannabidiol are those with intellectual disabilities and developmental delays. Additionally, patients with neuropsychiatric comorbidities could also benefit from cannabidiol, as it may improve neuropsychiatric symptoms, while other available ASMs may worsen these symptoms. The experts also noted that these patients would be easily identifiable by clinicians based on the patients' seizures and comorbidities. The clinical experts emphasized that caution and monitoring should be taken in patients with history of depression and with liver disease, particularly for patients taking concomitant valproate. Additionally, dose adjustment may be required in patients who are taking concomitant clobazam and mTOR inhibitors due to the changing levels of desmethylclobazam and increased mTOR levels due to the administration of cannabidiol. Additionally, there is no established safety in pregnancy, which would be a consideration for patients of childbearing age.

The clinical experts highlighted that measures of seizure frequency and severity remain the most important consideration of treatment. Additional assessments in real-world practice include hospitalizations, rescue medication use, and side effects of treatment. The clinical experts also agreed that though important, QoL measurements, caregiver burden, increase in independence, and clinical global impression are not commonly used in clinical practice, though the subjective experience of patients is used to inform treatment decisions. The clinical experts highlighted that despite the 50% responder threshold used in the trial, even a 25% to 30% reduction in seizure frequency may be beneficial if there is reduction in the most severe and disabling type of seizures (i.e., tonic-clonic seizures). Initially, patients with TSC-associated seizures would be seen as often as every 3 months to monitor treatment and perform any medication adjustments, though patients are mostly seen every 6 months. For patients who are seizure free, annual assessments would be conducted. When deciding to discontinue treatment, the clinical experts agreed that treatment would be discontinued in patients who experience severe adverse events (AEs) such as elevation of liver enzymes of more than 5 times the limit, severe sedation, nausea, and allergic reaction. Additionally, worsening of neuropsychiatric side effects such as depression should also be a reason for discontinuation. The clinical experts also stated that some medications can interact with cannabidiol (e.g., valproic acid and clobazam) and may need to be adjusted before considering discontinuation. The experts noted that use of additional rescue medication would not prompt discontinuation of treatment, given that this is generally used to break a cluster of seizures or a continuous prolonged seizure.

Clinician Group Input

No clinician group input was received by CADTH for this review.

Drug Program Input

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
Relevant Comparators	
The phase III, double-blind CARE6 trial evaluated the efficacy and safety of Epidiolex plus usual care vs. usual care alone (i.e., placebo). Currently, everolimus is the only drug indicated for TSC-associated seizures in Canada and was approved by Health Canada for adjunctive treatment of seizures associated with TSC in patients 2 years and older, with a definite diagnosis of TSC, who are not satisfactorily controlled with current therapies. However, everolimus for TSC-associated epilepsy has not been reviewed by CADTH. Everolimus was not included as a comparator within the submission, and patients receiving mTOR inhibitors were excluded from the CARE6 trial. Should everolimus be considered a comparator for Epidiolex?	CDEC and the clinical experts noted that though everolimus has Health Canada approval as adjunctive treatment of seizures associated with TSC in patients 2 years and older, the primary indication and use of this therapy is as a chemotherapy for tumour shrinkage and is fundamentally a different class of treatment. As a chemotherapy, patients must remain on therapy otherwise tubers can regrow. Despite some evidence of seizure frequency reduction, it would not be solely used for seizure control.
Considerations for Initiation of Therapy	
TSC can be diagnosed via clinical findings (e.g., cutaneous manifestations) or genetic testing, though genetic testing was not a requirement in the CARE6 trial to diagnose TSC. Pathogenic variants of TSC1 and TSC2 provide a definite diagnosis in 85 to 90% of patients. How accessible is genetic testing for TSC across Canada, and is genetic testing typically conducted on patients in Canada to confirm diagnosis?	Genetic testing for TSC is widely available to patients in Canada, however, confirmation of a diagnosis by genetic testing is not necessary for TSC. The clinical experts highlighted that TSC is most commonly diagnosed by various clinical markers including the presence of tubers, skin lesions, and confirmed by imaging (e.g., CT/MRI). Though genetic testing is widely available, some families choose not to proceed with genetic testing for personal, ethical, or other reasons. Regardless, CDEC agreed with the clinical experts that the results of genetic testing would not affect treatment decisions for patients with TSC-associated seizures.
Patients in the CARE6 trial were required to have a documented history of epilepsy, which was not completely controlled by their current ASMs, and patients were required to be taking at least one ASM at a dose which had been stable for at least 4 weeks. The inclusion criteria for the CARE6 trial did not require patients to have failed 1 or more ASM prior to enrollment. Oxcarbazepine has a higher threshold of initiation of coverage, requiring 1 to 3 ASMs to have failed. Would you initiate cannabidiol in patients who were currently undergoing treatment with only 1 ASM?	CDEC and the clinical experts highlighted that by definition, cannabidiol used as adjunctive treatment would be at least the second therapy attempted. The current standard of care requires careful consideration of treatment sequencing to optimize the balance of harms and effects. CDEC and the clinical experts noted that other ASMs may be restricted to 2 or 3 prior attempts to control seizures, thus, a setting a precedent, and it would be reasonable to have similar limitations in place for cannabidiol. The current criteria of 3 prior ASM failures for oxcarbazepine is a barrier as this could be high for some patients who are less refractory. Though no guidance exists on this issue, prescribers may initiate cannabidiol after at least 2 ASMs have been tried.
Considerations for continuation or renewal of therapy	
Most ASMs are open-benefit, and no specific guidance is provided in terms of renewal criteria. A reduction in seizures is a relevant and clinically meaningful outcome for patients with TSC-	In clinical practice, therapeutic response is measured via seizure count, and seizure severity. Quantifying seizure severity is difficult and not routinely done in clinical trials.

Drug Program Implementation Questions	Response
associated epilepsy and successful therapy is determined by a reduction in seizure frequency. What objective measures are used in routine clinical practice to assess therapeutic response in patients with TSC-associated seizures?	Quality of life of patients is another metric that is considered by treating physicians, though no specific QoL tools are generally used in practice, rather patients and caregivers provide their own overall assessment of how their QoL has changed (i.e., increase or decrease in seizure frequency/severity, increased alertness, etc.).
Considerations for discontinuation of therapy	
How would loss of response or absence of clinical benefit be defined in patients with TSC-associated seizures?	CDEC and the clinical experts agreed that loss or lack of response are also measured by seizure count and severity as reported by patients.
Most of the patients in the CARE6 trial experienced side effects. There were no defined metrics provided for discontinuation of the drug. In what circumstances would Epidiolex be discontinued?	CDEC and the clinical experts agreed that cannabidiol should be discontinued in patients who experience intolerable side effects from treatment, including but not limited to significant elevations in liver enzymes, sedation, significant GI side effects, and hypersensitivity reactions.
Considerations for prescribing of therapy	
The dosing of cannabidiol in the CARE6 trial (25mg/kg/day and 50mg/kg/day) was not reflective of the dosing criteria for TSC (10 to 25mg/kg/day) in the Product Monograph. There is potential for prescribers to increase the dose to those used in the clinical trials, impacting cost. Would you prescribe cannabidiol beyond the indicated dosage?	The CARE6 trial evaluated the dose of 50 mg/kg/day, which is not currently indicated for this population, and was noted by the clinical experts to be high for this type of medication. CDEC and the clinical experts noted that no observable dose-response relationship was observed in terms of efficacy thus, it is unlikely that prescribing cannabidiol beyond the indicated dosage would be done. If conducted, dosing beyond the Health Canada approved dosage of 25 mg/kg/day would be dependent on tolerability of treatment.
It is expected that Epidiolex would be prescribed by neurologists with expertise in managing seizures. There may be limited access to neurologists within some regions. How could patients without access to specialized care receive treatment with Epidiolex?	CDEC and the clinical experts highlighted that patients with TSC-associated seizures are under the care of neurologists with expertise in the treatment of epilepsy. Patients are required to see a specialist in order to be prescribed treatment for TSC-associated seizures, though administration of treatment is not a concern, and does not need to be done in specialized centers. Recently, virtual care has become more common, and should assist with treatment monitoring.
Cannabidiol is available as an amber liquid with 100mg/mL in a 100 mL bottle. Patients are titrated to effective therapeutic dose during the first 2 weeks of therapy. The patient or caregiver is required to measure the dose.	No response required. For CDEC consideration.
This product is intended to be used as adjunctive therapy to current ASMs. Cannabidiol is a potent CYP3A4 and CYP2C19 inhibitor. It is known to increase drug levels of clobazam, rufinamide and topiramate. More information about drug interactions would be beneficial.	No response required. For CDEC consideration.
Generalizability	
The CARE6 trial was a multi-site, randomized, double-blind, placebo-controlled trial. Patients on mTOR inhibitors (everolimus), and patients who already were taking (medical) cannabis products were excluded from the trial. Would you consider using Epidiolex in these patients?	CDEC and the clinical experts highlighted that there is no evidence to support the use of cannabidiol in these patients.

Drug Program Implementation Questions	Response
Medical cannabis is used to treat refractory or drug resistant epilepsy. It is expected that patients would prefer to switch to a pharmaceutical grade alternative for varying reasons (consistent product availability/quality, pharmacist involvement/medication review, and coverage by public/private insurers [currently only VAC and some private insurers cover medical cannabis products]). Are there any challenges related to using the medical cannabis pathway supported by Health Canada? Do you foresee other patients with drug resistant epilepsy wanting access to Epidiolex?	Most patients with TSC-associated seizures who use medical cannabis incur significant out of pocket costs, as it is not generally covered by most plans. As such, if there is no coverage available for cannabidiol, the clinical experts stated that patients are unlikely to switch due to cost constraints. However, some patients/caregivers may be interested in switching to cannabidiol as it is a "natural" product, though this perception may shift because it is a pharmaceutical product.
Care provision issues	
In the CARE6 trial, 94 to 100% of patients experienced AEs, most commonly diarrhoea, decreased appetite, somnolence, and vomiting, which were largely resolved by the end of the study and did not result in many patients discontinuing the drug. The most common reason for discontinuation was elevated transaminases and rash. Other noteworthy harms included a greater than 5% decrease in weight in nearly 31% of cannabidiol 25 mg/kg/day compared to 8.4% in the placebo group. How significant are the side effects for cannabidiol when compared to alternative ASMs? Are there any concerns with cannabidiol that may impact growth or development, and do patients with TSC-associated seizures already have challenges with nutritional intake (i.e., requiring nutritional support such as meal replacements, tube feeds, or TPN) given the weight loss observed in the trial?	Overall, the distribution of AEs in the CARE6 trial was not notably different to the AE profile of other ASMs. The key consideration with the individual AEs experienced in the CARE6 trial is whether they led to discontinuation of treatment. Considering that the overall discontinuation due to GI events was low, the instance of this in clinical practice may not be a concern. Regarding weight loss, a 5% decrease in weight is likely not actionable and wouldn't prompt discontinuation of treatment. CDEC and the clinical experts noted that there is a concern about the impact of cannabidiol on the developing brain, however, the mechanism and impact of this is not fully understood, so patients would be carefully monitored. Additionally, these patients already have a significant brain disorder, thus, the advantages of cannabidiol currently outweigh the risks.
System and economic issues	
The submitted list price is $1,424.5400 per 100 mL bottle, extrapolated to an annual cost of $102,200 for an adult at the maximum recommended therapeutic dose. Note: the study dose went to a maximum of 50mg/kg/day. The sponsors BIA estimated the reimbursement of Epidiolex will result in an incremental cost of $911,156 in Year 1, $2,022,989 in Year 2, $3,397,821 for Year 3, for a cumulative three-year budget impact of $6,331,966. They assumed an 85% compliance rate and did not account for wastage when using a multidose bottle.	No response required. For CDEC consideration.
Cannabidiol is an adjunctive therapy and therefore, there are other ASM medication costs to be considered. There was no information provided with regards to changes to usual care (dose reductions or discontinuation of current ASMs).	No response required. For CDEC consideration.

AE = adverse event; ASM = anti-seizure medication; BIA = budget impact analysis; CADTH = Canadian Agency for Drugs and Technologies in Health; CDEC = Canadian Drug Expert Committee; CT = computed tomography; MRI = magnetic resonance imaging; mTOR = mammalian target of rapamycin; TSC = tuberous sclerosis complex.

Clinical Evidence

Systematic Review

Description of Studies

One phase III placebo-controlled randomized controlled trial (RCT) (CARE6; N = 224) evaluated the reduction in seizure frequency of cannabidiol oral solution versus placebo as an adjunctive treatment for the treatment of seizures in children and adults with TSC which was not completely controlled by their current ASMs. Patients were randomized 2:2:1:1 to cannabidiol 25 mg/kg/day (N = 75), cannabidiol 50 mg/kg/day (n = 73), and 2 matching dose-volume equivalent placebo groups (pooled N = 76), for 16 weeks. The cannabidiol 50 mg/kg/day group is not a recommended dosage per the Health Canada and was not included in this report. Following completion of the double-blind treatment period, patients then had the option to enter the long-term, open-label extension (OLE) study.

Baseline characteristics were generally balanced across treatment groups, with a mean age of 13.7 years (25 mg/kg/day, 14.1 years vs. Placebo, 13.9 years); there were a few baseline imbalances that were compatible with chance. All patients had TSC-associated seizures, with Type 2 focal seizures occurring most frequently in each group (25 mg/kg/day, 46 [61.3%] vs. Placebo, 50 [65.8%]), followed by Type 1 Focal Motor (25 mg/kg/day, 29 [38.7%] vs. Placebo, 33 [43.4%]). The mean number of TSC-associated seizures during the baseline period was 77.95 (standard deviation [SD], 83.39; range, 7.7 to 427.7) in the cannabidiol 25 mg/kg/day group and 89.22 (SD, 101.78; range, 8.0 to 558.0) in the placebo group. The median number of concurrent ASMs in each treatment group was 3 (range, 0 to 5), while the median number of prior ASMs that were no longer being taken was 4 (range, 0 to 15).

Efficacy Results

Percent Change from Baseline in Seizure Frequency

The primary endpoint of CARE6 was the change from baseline in the number of TSC-associated seizures during the treatment period. The mean percent change from baseline with cannabidiol 25 mg/kg/day was 48.6% (95% confidence interval [CI], 40.4% to 55.8%) compared to and 26.5% (95% CI, 14.9% to 36.5%) for placebo. The ratio of cannabidiol to placebo was 0.699 (95% CI, 0.567 to 0.861) which translated to an estimated relative reduction for cannabidiol 25 mg/kg/day compared to placebo of 31.0% (95% CI, 13.9% to 43.3%; p = 0.0009).

Results of subgroup analyses were consistent with the primary analysis, though the reductions in seizure frequency observed in patients currently taking clobazam appeared larger than those not taking clobazam, the 95% CIs overlap.

Treatment Responders: Proportion of Patients with ≥ 25% Reduction in Seizure Frequency, ≥ 50% Reduction in Seizure Frequency, and Total Seizure Freedom

The proportion of patients with a greater than or equal to 50% reduction from baseline in TSC-associated seizure frequency was the first key secondary endpoint of CARE6. In the double-blind treatment period, 27 (36.0%) patients in the cannabidiol 25 mg/kg/day group and 17 (22.4%) patients in the pooled placebo group experienced a 50% or more reduction in seizure frequency cannabidiol 50 mg/kg/day (odds ratio [OR], 1.95 [95% CI, 0.95 to 4.00; p = 0.0692]). The difference in proportion of patients achieving a 50% or greater reduction in TSC-associated seizure frequency between cannabidiol 25 mg/kg/day compared to placebo was 13.6% (95% CI, -0.7 to 28.0).

The proportion of patients with a reduction in TSC-associated seizure frequency by at least 25% and seizure freedom (100% reduction in seizure frequency) were secondary endpoints of the CARE6 trial. In the treatment period, 43 (57.3%) and 33 (43.4%) patients in the cannabidiol 25 mg/kg/day and placebo groups experienced a 25% or greater reduction in seizure frequency, respectively (OR, 1.75 [95% CI, 0.92 to 3.33]). The difference in the proportion of patients achieving a 25% or greater reduction in TSC-associated seizure frequency between cannabidiol 25 mg/kg/day compared to placebo was 13.9% (95% CI, -1.9% to 29.7%). Only 1 (1.3%) patient in the cannabidiol 25 mg/kg/day group experienced seizure freedom during the treatment period.

Health-Related Quality of Life

Health-related quality of life was assessed using the Quality of Life in Childhood Epilepsy (QOLCE) in pediatric patients aged 2 to 18 years old and the Quality of Life in Epilepsy (QOLIE)-31-P in patients aged 19 years and older. For both measures, the overall scores were calculated from 0 to 100, with higher scores representing better HRQoL.

Change from Baseline in QOLCE Scores

An overall QoL score for the QOLCE was available for 45 patients in the cannabidiol 25 mg/kg/day group at baseline compared to 42 patients at the end of treatment. For the placebo group, 50 patients had an overall QoL score for the QOLCE at baseline compared to 47 at the end of treatment. At the end of treatment, the least squares (LS) mean change from baseline was 3.1 points (95% CI, -0.6 to 6.7), and 1.6 points (95% CI, -1.8 to 4.9), in the cannabidiol and placebo groups, respectively. The LS mean difference between groups in change from baseline was 1.5 points (95% CI, -3.3 to 6.3 points).

Change from Baseline in QOLIE-31-P Scores

The QOLIE-31-P was completed by 13 patients in the cannabidiol 25 mg/kg/day group and 10 patients in the placebo group at baseline, and 14 patients in the cannabidiol 25 mg/kg/day group and 12 patients in the placebo group at the end of treatment. At the end of treatment, the LS mean change from baseline was -1.4 points (95% CI, -16.2 to 13.5), and 2.3 points (95% CI, -15.0 to 19.7), in the cannabidiol and placebo groups, respectively. The LS mean difference between groups in change from baseline was -3.7 points (95% CI, -16.6 to 9.2 points).

Rescue Medication Use

During the baseline period, the number of days of rescue medication use in the cannabidiol 25 mg/kg/day group and placebo groups was 2.14 days (SD, 2.187) and 2.32 (SD, 3.200), respectively. The mean number of days of rescue medication use during the treatment period was 0.79 days (SD, 2.469) in the cannabidiol 25 mg/kg/day group and 0.55 days (SD, 1.395) in the placebo group, representing mean changes from baseline of 0.19 days (SD, 2.836) and -0.92 days (SD, 1.858), respectively. The mean difference in change from baseline in rescue medication use days between cannabidiol 25 mg/kg/day compared to placebo was 0.96 (95% CI, -0.65 to 2.56).

Status Epilepticus

During the baseline period, no patients in the cannabidiol 25 mg/kg/day group had status epilepticus, compared to 3 (3.9%) patients in the placebo groups. The proportion of patients who reported episodes of status epilepticus during the treatment period was 6.7% in the cannabidiol 25 mg/kg/day group and 9.2% in the placebo group.

Vineland II Adaptive Behaviour Scale

At the end of treatment, the mean adaptive behaviour composite score in the cannabidiol 25 mg/kg/day and placebo groups was 50.7 (SD, 22.24), and 51.5 (SD, 25.57), respectively, representing a LS mean change from baseline of -0.0 points (95% CI, -1.6 to 1.5) for cannabidiol 25 mg/kg/day, and -0.0 points (95% CI, -1.6 to 1.5) for placebo. The difference in LS mean change from baseline was 0.0 points (95% CI, -2.2 to 2.1 points).

Harms Results

At least 1 treatment emergent adverse event (TEAE) was reported by 70 (93.3%) patients in the cannabidiol 25 mg/kg/day group and 72 (94.7%) patients in the pooled placebo group. The most frequently occurring TEAEs (10% of patients or more) in the cannabidiol 25 mg/kg/day group were diarrhea (23 [30.7%]), decreased appetite (15 [20.0%]), pyrexia (14 [18.7%]), vomiting (13 [17.3%]), increased gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) (12 [16.0%], 9 [12.0%], 8 [10.7%], respectively), and somnolence (10 [13.3%]), and cough (8 [10.7%]). In the pooled placebo groups, the most frequently occurring TEAEs were diarrhea (13 [17.1%]), nasopharyngitis (12 [15.8%]), upper respiratory tract infection (10 [13.2%]), and decreased appetite (9 [11.8%]).

A total of 28 (12.5%) patients in the CARE6 trial experienced a total of 44 serious adverse events (SAEs); 16 (21.3%) in the 25 mg/kg/day group, and 2 (2.6%) in the pooled placebo group. The most commonly reported individual SAEs in the cannabidiol 25

mg/kg/day group were increased ALT (2 [2.7%]), increased AST (2 [2.7%]), status epilepticus, vomiting, and viral gastroenteritis (2 [2.7%] each). Serious AEs in the placebo group only occurred in 2 (2.6%) patients and included pneumonia and status epilepticus (1 [1.3%] each).

A total of 20 (8.9%) patients had TEAEs leading to discontinuation of treatment; 8 (10.7%) in the 25 mg/kg/day group, and 2 (2.6%) in the pooled placebo group. The most common reason for discontinuing treatment in the cannabidiol group was rash (2 [2.7%]). All other reasons for discontinuation occurred in only 1 (1.3%) patient. The 2 patients in the placebo groups discontinued treatment due to TEAEs of ataxia and agitation, respectively.

There were no deaths reported during the CARE6 trial.

Notable Harms

Adverse events of special interest (AESI) to this review consisted of hepatocellular injury, and hypersensitivity reactions. In the cannabidiol 25 mg/kg/day group, liver injury and type IV hypersensitivity reactions occurred in 1 (1.3%) each and were listed as SAEs and both led to discontinuation of treatment.

Critical Appraisal

The phase III CARE6 trial was the only study included in this review. Randomization was stratified by age, however, given the known interaction between clobazam and cannabidiol, failure to stratify by clobazam use was a limitation, though the CARE6 trial was initiated before the importance of this interaction was known. It remains unclear what impact this may have had on the distribution of patients in the trial, and how the results may have been impacted. There were some baseline imbalances, however the clinical experts consulted by CADTH noted that there is substantial disease heterogeneity in this population, and they agreed that the differences could be due to chance. There were also differences across the cannabidiol 25 mg/kg/day and placebo groups in discontinuation of study treatment (13.3% vs. 1.3%), primarily due to AEs (10.7% vs. 0.0%). Despite being a double-blind RCT, this may have revealed treatment assignment; however, it is unclear what effect this would have on the results of the study. Most outcomes in the CARE6 trial were related to seizure frequency, which was measured by countable seizures of various types. In consultation with clinical experts, there is some subjectivity and error in how patients and caregivers may classify these, however, the seizure types defined for the trial are generally countable and should not ultimately bias the results. Subgroups of interest to this review included clobazam use, and the number of concurrent and prior ASMs based on discussion with the clinical experts consulted by CADTH. Results generally supported the primary analysis, though they were not statistically powered to detect within-group, or between-group differences. Additionally, wide overlapping 95% CIs reflected uncertainty in the effect estimates and were likely due to the small sample sizes, thus, the results should be viewed as supportive evidence for the overall effect of cannabidiol. Outcomes related to HRQoL were considered important to patients and were captured as other secondary endpoints of CARE6. The QOLCE and QOLIE-31-P were considered reliable and valid measures for epilepsy in TSC, though the clinical experts consulted by CADTH noted that these are not used in routine clinical practice. The use of rescue medication and change in rescue medication use days was an exploratory outcome of CARE6. Most patients required the use of rescue medication at some point during the treatment period, though rescue medication usage was not accounted for in the primary or key secondary endpoint analyses, thus it remains unclear whether there was any impact of rescue medication on the results. As noted by the clinical experts, the use of rescue medication would not prompt discontinuation of therapy.

Two dosages of cannabidiol were evaluated in the CARE6 trial: 25 mg/kg/day and 50 mg/kg/day, however, given that the maximum recommended Health Canada approved dosage of cannabidiol for TSC-associated seizures is 12.5 mg/kg twice daily (25 mg/kg/day), the cannabidiol 50 mg/kg/day dose was not of interest to this review. CARE6 was an international multicenter study, however, there were no Canadian sites included. As part of the inclusion and exclusion criteria for the CARE6 trial, patients were required to have a clinical diagnosis of TSC. Genetic confirmation was not required, which was noted by the clinical experts consulted by CADTH to be consistent with clinical practice. The included population had a high seizure burden and particularly drug-resistant epilepsy demonstrated by the baseline seizure frequency (range, 8 to 558) and number of prior (range, 0 to 15) and concurrent ASMs (range, 0 to 5). The clinical experts consulted by CADTH noted that the included population was reflective of clinical practice, highlighting that there is often variability in seizure burden across patients; however, it was highlighted that not all patients with TSC have such high disease burden, thus the enrolled population may have been restrictive, selecting for patients with more refractory epilepsy and higher disease burden. Additionally, there was heterogeneity in the concomitant ASMs received by

patients in the CARE6 trial, however, the clinical experts consulted by CADTH noted that this is in line with clinical practice and varies by patient based on response, intolerance, and various contraindications. Outcomes in the CARE6 trial were considered clinically relevant and important to patients, mainly focusing on measures of seizure frequency, which is the focus of epilepsy treatment in routine clinical practice. However, an additional consideration as noted by patient groups and the clinical experts consulted by CADTH is the reduction in seizure severity, which was not explicitly measured in the CARE6 trial. The clinical experts consulted by CADTH highlighted that a reduction in the frequency of seizures may not necessarily be associated with a reduction in severity. The duration of the CARE6 trial at 16 weeks was considered appropriate for measuring response to treatment and observing changes in seizure frequency. However, given that the impact of cannabidiol on HRQoL and TANDs were also outcomes of interest to this review, and the secondary nature of these outcomes, the small sample sizes for completion of various measures, and the short duration of the CARE6 trial are difficult to interpret. As such, these outcomes should only be viewed as supportive of the overall effect of cannabidiol.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

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

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: the percent change from baseline in the number of TSC-associated seizures at week 16, the proportion of patients considered treatment responders (i.e., achieving target reductions of 25% or 50% more) or achieving seizure freedom (100% reduction in seizure frequency) at week 16, improved HRQoL as assessed by the change from baseline in QOLCE and QOLIE-31-P scores at week 16, the proportion of patients with status epilepticus at week 16, the change from baseline in rescue medication use days at week 16, and the change from baseline in Vineland II adaptive behaviour scale at week 16; proportion of patients with at least one SAE, proportion of patients with hepatocellular injury.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment was the presence of a clinically important reduction in seizure frequency (percent change in seizure frequency) on thresholds informed from clinical expert opinion, treatment guidelines, and clinical trials, as well as HRQoL and patient reported outcome (QOLCE, QOLIE-31-P, Vineland II) assessments informed by the literature where available. Other targets for the certainty of evidence assessment were the presence or absence of any (non-null) effect for the proportion of patients achieving 25%, 50% or 100% reductions in seizure frequency, the proportion of patients with status epilepticus, and changes from baseline in rescue medication use.

Results of GRADE Assessments

Table 2 presents the GRADE summary of findings for cannabidiol vs. placebo for outcomes in the pivotal CARE6 trial.

Table 2: Summary of Findings for Epidiolex Versus Placebo as an Adjunctive Treatment for Patients With TSC-Associated Seizures

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Cannabidiol	Difference		
Change in Seizure Frequency							
Percent Change from Baseline in TSC-Associated Seizure Frequency Follow-up: 113 Days	151 (1 RCT)	Ratio 0.699 (0.57 to 0.86), expressed as % reduction: 31.0% (13.9 to 43.3%)	26.5 per 100 (14.9 to 36.5 per 100)	48.6 per 100 (40.4 to 55.8 per 100)	22.1 per 100 fewer (NR)	Moderate[a]	Cannabidiol likely results in a clinically important decrease (improvement) in seizure frequency when compared with placebo.
Percent of Patients with ≥50% Reductions in TSC-Associated Seizure Frequency Follow-up: 113 Days	151 (1 RCT)	OR, 1.95 (0.95 to 4.00)	22.4 per 100	36.0 per 100	13.6 per 100 more (0.7 fewer to 28.0 more per 100)	Moderate[b]	Cannabidiol likely results in a greater proportion of patients achieving a 50% reduction in TSC-associated seizure frequency when compared with placebo. The clinical importance of the reduction is unclear.
Percent of Patients with ≥25% Reductions in TSC-Associated Seizure Frequency Follow-up: 113 Days	151 (1 RCT)	OR, 1.75 (0.92 to 3.33)	43.4 per 100	57.3 per 100	13.9 per 100 more (1.9 fewer to 29.7 more per 100)	Moderate[b, c]	Cannabidiol likely results in a greater proportion of patients achieving a 25% reduction in TSC-associated seizure frequency when compared with placebo. The clinical importance of the reduction is unclear.
Percent of Patients with Seizure Freedom (100% Reductions in TSC-Associated Seizure Frequency) Follow-up: 113 Days	151 (1 RCT)	OR, NE	0 per 100	1.3 per 100	1.3 per 100 (1.3 fewer to 3.9 more per 100)	Moderate[b, c]	Cannabidiol likely results in little to no difference in the proportion of patients achieving total TSC-associated seizure freedom (100% reduction in seizure frequency) when compared with placebo. The clinical importance of the effects is uncertain.
Status Epilepticus and Need for Rescue Medication							

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Cannabidiol	Difference		
Proportion of Patients with Status Epilepticus Follow-up: 113 Days	151 (1 RCT)	NA	9.2 per 100	6.7 per 100	2.5 fewer per 100 (11.2 fewer to 6.1 more per 100)	Low[c, d]	Cannabidiol may result in little to no difference in the proportion of patients with status epilepticus when compared with placebo. The clinical importance of the effects is uncertain.
Mean Change from Baseline in Rescue Medication Use Days (Per 28 Days) Follow-up: 113 Days	151 (1 RCT)	NA	-0.92 (SD, 1.86)	0.19 (SD, 2.84)	0.96 (−0.65, 2.56)	Low[c, d]	Cannabidiol may result in little to no difference in the rescue medication use when compared with placebo. The clinical importance of the effects is uncertain.
Quality of Life and Adaptive Behaviour							
Change from Baseline in QOLCE Overall QoL Score, points Follow-up: 113 Days	82 (1 RCT)	NA	1.6 (-1.8, 4.9)	3.1 (-0.6, 6.7)	1.5 (-3.3, 6.3)	Very low[c, e]	The effect of cannabidiol on QOLCE overall QoL score when compared with placebo is very uncertain.
Change from Baseline in QOLIE Total Score, points Follow-up: 113 Days	22 (1 RCT)	NA	2.3 (-15.0, 19.7)	-1.4 (-16.2, 13.5)	-3.7 (-16.6, 9.2)	Very low[c, f]	The effect of cannabidiol on QOLIE total score when compared with placebo is very uncertain.
Change from Baseline in Vineland II Adaptive Behavior Composite Score, points Follow-up: 113 Days	90 (1 RCT)	NA	0.0 (-1.6, 1.5)	0.0 (-1.6, 1.5)	0.0 (-2.2, 2.1)	Very low[c, g]	The effect of cannabidiol on the Vineland II Adaptive Behaviour Composite score when compared with placebo is very uncertain.
Harms[h]							
Hepatocellular injury (Safety endpoint) Follow-up: 113 Days	151 (1 RCT)	NA	0 per 100	1 per 100	1.33 more per 100 (1.26 fewer to 3.93 more per 100)	Moderate[i]	Cannabidiol likely results in little to no difference in the proportion of patients with hepatocellular injury versus placebo. The clinical importance of the effects is uncertain.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Cannabidiol	Difference		
SAEs Follow-up: 113 Days	151 (1 RCT)	NA	3 per 100	21 per 100	18.7 more per 100 (8.76 to 28.65 more per 100)	Low[j]	Cannabidiol may result in an increase in the proportion of patients with SAEs versus placebo. The clinical importance of the difference is uncertain.

CI = confidence interval; NA = not available; NE = not estimable; QOLCE = quality of life in childhood epilepsy; QOLIE = quality of life in epilepsy; RCT = randomized controlled trial; SAE = serious adverse event; TSC = tuberous sclerosis complex.

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

[a] Rated down 1 level for serious imprecision. The 95% CI included the potential for no clinically meaningful benefit. Based on clinical expert opinion, a threshold of about a 25% reduction in seizure frequency could be considered meaningful, and any reduction not reaching this threshold would be difficult to quantify. The 95% CI on the relative effect suggests a wide range of effects with the lower bound being potentially not clinically important.

[b] Rated down 1 level for serious imprecision. Using the null as the threshold, the 95% CI is compatible with both a benefit and little-to-no difference.

[c] Statistical testing for this outcome was not adjusted for multiplicity in the trial and should be considered as supportive evidence.

[d] Did not rate down for risk of bias. Though there were notable and imbalanced withdrawals from the study, it is not clear at which time these patients would have stopped contributing to the analysis. Rated down 2 levels for imprecision. Using the null as the threshold, the 95% CI is compatible with both benefit and harm.

[e] Rated down 2 levels for very serious risk of bias due to a large quantity of missing outcome data. Rated down 1 level for serious imprecision. Based on the reported MID of 2.9 to 6.0 points, the 95% CI is compatible with little-to-no difference and benefit.

[f] Rated down 2 levels for very serious risk of bias due to a large quantity of missing outcome data. Rated down 1 level for serious imprecision. Based on the reported MID of 7.1 to 11.0 points, the 95% CI is compatible with little-to-no difference and harm.

[g] Rated down 2 levels for very serious risk of bias due to a large quantity of missing outcome data. Rated down 2 levels for very serious imprecision. Using the null as the threshold, the 95% CI includes the potential for both benefit and harm. Rated down 1 level for serious indirectness due to insufficient duration of follow-up to adequately assess this outcome, based on clinical expert opinion.

[h] This result was not part of the sponsor's prespecified analysis plan and was requested by CADTH to assist in interpretation of the findings.

[i] Rated down 1 level for serious imprecision. Using the null as the threshold, the 95% CI is compatible with both little-to-no difference and harm.

[j] Rated down 2 levels for very serious imprecision. The effect is informed by a small number of events and may be unstable.

Source: CARE6 Clinical Study Report.

Long-Term Extension Studies

Description of Studies

One open-label, single-arm, long-term extension of the CARE6 study (CARE6 OLE) was summarized to provide evidence regarding long-term safety and efficacy of cannabidiol. Upon completion of the double-blind phase of the CARE6 study, 199 patients who had completed the double-blind phase were invited to receive open label cannabidiol during the OLE period for a maximum duration of 4 years (124 from cannabidiol 25 mg/kg/day and 50 mg/kg/day groups, and 75 from the placebo group). The primary outcome of the CARE6 OLE study was to evaluate the AEs profile (long-term safety and tolerability) of cannabidiol. Secondary outcomes of interest to this review were in line with the outcomes evaluated during the double-blind period of CARE6.

Efficacy Results

In the OLE study, maintenance of efficacy was assessed in 156 patients treated for 37 to 48 weeks to account for differences in sample sizes with increasing time. The median percent reduction in TSC-associated seizure frequency from baseline was -66.27% (IQR, -86.70% to -18.64%) during weeks 37 to 48 of treatment, and a median -55.22% (IQR, -81.70% to -13.47%) change throughout the entire OLE treatment period (n = 199).

The number of patients who achieved a ≥50% reduction in TSC-associated seizure frequency at 37 to 48 weeks of treatment was 93 (60%), and 106 (53%) throughout the entire OLE treatment phase. There were no notable differences in proportion of patients achieving a ≥50% reduction in TSC-associated seizure frequency between patients who had been treated with cannabidiol vs. placebo during the double-blind phase of the study (60.0% vs. 59.0%).

Patients experienced a reduction in the overall QOLIE-31-P (patients ≥ 19 years) total score relative to the pre-randomization baseline of the double-blind phase, with a mean change from baseline of -9.0 (SD, 17.99) for all patients (n = 9) and -7.4 (SD, 18.57) for patients aged ≥19 years (n = 8) at OLE end of treatment. Based on a change from double-blind phase baseline to OLE end of treatment, a reduction in the QOLIE-31-P total score was observed in the cannabidiol cohort (-14.8 [SD, 20.60]; n = 5) and the placebo cohort (-1.8 [SD, 13.2]; n = 4). For patients aged ≥19 years (n = 8), QOLIE-31-P total score reduction was -13.1 (SD, 23.39; n = 4) in cannabidiol cohort vs.-1.8 (SD, 13.12; n = 4) in placebo cohort.

Based on a change from double-blind baseline to OLE end of treatment, a reduction in mean number of days of rescue medication use was -0.44 (SD, 4.09) in total population (n = 55): -0.10 (SD, 4.73) in cannabidiol cohort (n = 35) vs. -1.02 (SD, 2.64) in placebo cohort (n = 20).

The number of patients with status epilepticus was 5 (2.5%) during the baseline period and 20 (10.1%) during the OLE treatment period. The number of patients who experienced status epilepticus was similar between patients treated with cannabidiol vs. placebo during the double-blind phase of the CARE6 study.

Harms Results

A total of 192 (96.5%) patients treated with cannabidiol had 1 or more AEs during the OLE study. Most common TEAEs were diarrhea (46.7%), seizure (29.6%), and pyrexia (24.1%). SAEs were reported in 56 (28.1%) participants with TSC, with the most common SAEs experienced being seizure (8%), status epilepticus (5%), and dehydration (3%).

There were 18 (9%) participants with TSC that stopped treatment due to AEs, with the most common AEs leading to discontinuation being seizure (2%) and diarrhea (2%). One patient died 2 months after starting the open-label treatment of cannabidiol, though was considered unrelated to cannabidiol.

Critical Appraisal

There was no active comparator or placebo group in the CARE6 OLE study, thus, the safety and the efficacy data could not be used to draw any conclusion in relation to an appropriate comparator. Furthermore, the open-label design may bias the reporting of subjective endpoints, including AEs, SAEs, and TEAEs. Since completion of a pivotal trial was an eligibility criterion for the extension study, patients who discontinued those trials due to AEs or lack of response were excluded. This could result in a population of patients that were more tolerant of cannabidiol, which can lead to a selection bias as those not responding to treatment are less likely

to continue. Having a patient population more tolerant of cannabidiol can also lead to biased estimates related to AEs, potentially resulting in fewer and less severe AEs being reported. The sample size of CARE6 OLE study (N = 199) may not be sufficient to detect rare AEs. Only 17.1% of patients completed the study, and there was wide variation in follow-up duration for individuals. For several outcomes, the sample size was therefore very small and not representative of all patients who started the OLE period.

The CARE6 OLE study enrolled patients from multiple sites in different countries, however, there were no study sites in Canada. No evidence indicating a difference between the study population and the Canadian patients was identified in consultation with the clinical experts. Even though the median number of dosing days was 369.5 days (range, 95.0 days to 1,462 days) provides longer follow-up for AE assessment versus the double-blind phase of the CARE6 study, the proportion of patients who adhered to the cannabidiol during the longer follow-up was not reported. Thus, the study drug exposure among the patients in the OLE study was uncertain. About half of patients (46.7%) were taking the 50 mg/kg/day dose, which is not an approved dosing level and could have impacted the results. The remaining were taking the 25 mg/kg/day dose, which is the highest dose suggested in the product monograph.

Indirect Comparisons

No indirect evidence on the comparative efficacy or safety of cannabidiol in patients with TSC-associated seizures was submitted by the sponsor.

Studies Addressing Gaps in the Evidence from the Systematic Review

No studies addressing gaps in the systematic review evidence were submitted by the sponsor.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Patients 2 years of age and older with tuberous sclerosis complex (TSC) and a history of epilepsy that is inadequately controlled by their current anti-seizure medication (ASM) (i.e., patients who experience at least 8 seizures during a 28-day baseline period).
Treatment	Cannabidiol, in combination with usual care. Usual care was defined by a variety of ASMs, including sodium valproate, vigabatrin, levetiracetam, clobazam, lamotrigine, lacosamide, oxcarbazepine, topiramate, and carbamazepine.
Dose regimen	Recommended dose of cannabidiol is 5 mg/kg/day for 1 week, followed by a maintenance dosage of 10 mg/kg/day, up to a maximum of 25 mg/kg/day depending on individual response and tolerability.
Submitted price	Cannabidiol, 100 mg/mL oral solution: $1,424.54 per 100 mL bottle
Treatment cost	Annual per-patient cost of cannabidiol for patients aged 2 to 6 years, 7 to 11 years, 12 to 17 years, and over 18 years are $12,631, $20,036, $32,730, and $45,672, respectively.[a] Annual per-patient cost of usual care ranges from $1,238 to $2,540.
Comparator	Usual care
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (100 years)
Key data source	CARE6: phase III, randomized, double-blind, placebo-controlled trial (data cutoff: February 26, 2019).
Key limitations	• The submitted model does not reflect the full Health Canada indicated population for TSC. Effectiveness of cannabidiol + usual care was based on the CARE6 trial population, which enrolled patients who experienced at least 8 seizures during a 28-day period. The cost-effectiveness of cannabidiol in the full indicated population and among patients with fewer than 8 seizures per 28 days is unknown.

Component	Description
	• The model structure does not adequately reflect patient experience with TSC and how it is managed in clinical practice. Clinical experts noted that the thresholds used for the daily seizure frequency sub-health states do not accurately capture the health-related quality of life (HRQoL) associated with a seizure day. • The health state utility values adopted by the sponsor for patients with TSC are highly uncertain and may not reflect the preferences of those living in Canada. The majority of incremental QALYs gained with cannabidiol + usual care were accrued by caregivers, not patients with TSC. • The long-term relative effectiveness of cannabidiol plus + care compared to usual care alone is highly uncertain. Approximately 97% of the incremental benefit associated with cannabidiol was accrued after the trial period. • The sponsor's model assumes that all patients will receive a cannabidiol maintenance dose of 12 mg/kg/day. Based on the Health Canada monograph, patients may receive up to 25 mg/kg/day based on treatment response and tolerability. Efficacy data for cannabidiol in the sponsor's model reflect patients from the CARE6 trial who were randomized to receive 25 mg/kg/day. In this group, the mean maintenance dose at the end of treatment (week 16) was 23 mg/kg/day.
CADTH reanalysis results	• The CADTH base case was derived by making changes to the following model parameters: removing caregiver disutilities to align the analysis of HRQoL with the target patient population; and revising the mean maintenance dose of cannabidiol to 23 mg/kg/day based on the mean maintenance dose observed among patients enrolled in the 25 mg/kg/day arm of CARE6. • In the CADTH base case, cannabidiol + usual care was associated with an ICER of $295,503 per QALY gained compared to usual care alone (incremental costs: $277,023; incremental QALYs: 0.94). A price reduction of 63% for cannabidiol would be required for cannabidiol + usual care to be cost-effective compared to usual care alone at a willingness-to-pay threshold of $50,000 per QALY gained. • The cost-effectiveness of cannabidiol + usual care was sensitive to the inclusion of caregiver QALYs. In a scenario that included spillover utility decrements due to caregiver burden, the ICER of cannabidiol + usual care decreased to $169,662 per QALY gained (incr. costs: $278,484; incr. QALYs: 1.64) relative to usual care.

ASM = anti-seizure medication; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; incr. = incremental; LY = life-year; QALY= quality-adjusted life-year; TSC = tuberous sclerosis complex.

[a] Based on a mean maintenance dose of 12 mg/kg/day,

Budget Impact

CADTH identified the following limitations in the sponsor's base case: the full indicated population for TSC was not modelled; the NIHB population was inappropriately calculated; cannabidiol drug costs are uncertain and likely underestimated; and the proportion of patients eligible for public drug plan coverage is uncertain and may be underestimated.

CADTH conducted reanalyses of the BIA by aligning the eligible population with the Health Canada indication for TSC; adopting a maintenance dose of 23 mg/kg/day among patients treated with cannabidiol; and using 100% adherence in the calculation of drug costs. Based on the CADTH base case, the estimated budget impact associated with the reimbursement of cannabidiol as adjunctive therapy for the treatment of seizures associated with TSC is expected to be $3,930,164 in Year 1, $9,134,576 in Year 2, and $15,275,760 in Year 3, for a 3-year budgetary impact of $28,340,500.

CADTH conducted scenario analyses to address remaining uncertainty. If the reimbursement of cannabidiol is restricted to patients with drug-refractory TSC-associated epilepsy, the 3-year budget impact associated with reimbursing cannabidiol is expected to be $14,174,180. Assuming that the price of cannabidiol is reduced by 63%, the price reduction at which cannabidiol + usual care would be considered cost-effective at a WTP threshold of $50,000 per QALY gained, the 3-year budget impact associated with reimbursing cannabidiol is expected to be $10,542,666. The estimated budget impact is highly sensitive to narrowing the eligible population to an ASM-refractory subgroup, as well as to the price of cannabidiol.

CDEC Information

Members of the Committee:

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

Meeting date: February 29, 2024

Regrets:

3 expert committee members did not attend.

Conflicts of interest:

None