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## CADTH Reimbursement Recommendation

# 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.
**Final recommendation:** Reimburse with conditions

# Summary

## What Is the CADTH Reimbursement Recommendation for Epidiolex?

CADTH recommends that Epidiolex should be reimbursed by public drug plans as adjunctive therapy for the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients aged 2 years and older if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Epidiolex should only be covered for the treatment of patients who are aged 2 years and older with seizures caused by TSC despite receiving other antiseizure medications.

### What Are the Conditions for Reimbursement?

Epidiolex should only be reimbursed in patients who have at least 8 seizures over a 28-day period that are not controlled despite receiving 2 or more antiseizure medications if it is prescribed by physicians with experience in the diagnosis and management of patients living with TSC and if the cost of Epidiolex is reduced. Epidiolex should not be reimbursed for use in combination with mTOR inhibitors or recreational or medicinal cannabis.

### Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical trial (CARE6) demonstrated that treatment with Epidiolex, when added on to at least 1 antiseizure medication, reduces the frequency of TSC-associated seizures compared to placebo.
- Although many treatments are available, substantial morbidity still exists for patients with TSC-associated seizures. Epidiolex may meet some needs that are important to patients because it is another treatment option that reduces the number of seizures, which is an important outcome for patients with TSC.
- Based on CADTH's assessment of the health economic evidence, Epidiolex does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Epidiolex is estimated to cost the public drug plans approximately $28 million over the next 3 years. 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.

# Summary

## Additional Information

### What Are TSC-Associated Seizures?

TSC is a rare genetic disease that causes noncancerous tumours (known as *tubers*) to grow in many parts of the body, most commonly in the brain, heart, lungs, kidneys, skin, and eyes. Tubers that form in the brain often cause different types of seizures, which can be frequent, severe, and even fatal. TSC affects 1 in 5,000 to 10,000 births; however, the number of people with seizures caused by TSC is unknown.

### Unmet Needs in TSC

Although many antiseizure medications are available, there is still a need for safe treatments that further reduce the number and severity of seizures for patients who have seizures that are not controlled by their current medication.

### How Much Does Epidiolex Cost?

Treatment with Epidiolex is expected to cost approximately $12,631, $20,036, $32,730, and $45,672 annually for patients aged 2 to 6 years, 7 to 11 years, 12 to 17 years, and 18 years and older, respectively.

## 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 aged 2 years and older only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

TSC is a rare, multisystem disorder in which seizures of varying types are the most common neurologic manifestation of the disease, affecting up to 70% of patients. TSC-associated seizures generally begin during the first year of life and progress 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 antiseizure medication (ASM), treatment with cannabidiol resulted in added clinical benefit in TSC-associated seizure frequency compared with placebo. In the CARE6 trial, the mean percent reduction 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 difference in mean percent reduction in seizure frequency from baseline at 16 weeks of 31.0% (95% confidence interval [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% for patients receiving cannabidiol and 22.4% for those receiving placebo (odds ratio [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 with cannabidiol (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 reduction in seizure frequency; however, there was insufficient evidence to evaluate the effect of cannabidiol on seizure severity, total seizure freedom, and health-related QoL (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 willingness-to-pay (WTP) threshold of $50,000 per QALY gained for patients aged 2 years and older with TSC and a history of epilepsy that is inadequately controlled by their current 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:<br>1.1. 2 years of age or older<br>1.2. currently taking 1 or more ASMs at stable doses for at least 4 weeks before initiation. | Evidence from the CARE6 trial demonstrated a clinical benefit in 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 that had been stable for at least 4 weeks before 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:<br>2.1. at least 8 seizures per 28 days before initiation of cannabidiol<br>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 28-day baseline period, with at least 1 seizure occurring in at least 3 of the 4 weeks. During 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.<br>Patients in the CARE6 trial received 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, although in practice, most are usually 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. | This is to ensure that cannabidiol is being used safely in patients who are benefiting from treatment. | – |

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| **Prescribing** | | |
| 5. The patient must be under the care of a physician with expertise in the diagnosis and management of TSC. | Accurate diagnosis and management of patients with TSC-associated seizures is important to ensure that cannabidiol is 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:<br>6.1. in patients concurrently using mTOR inhibitors<br>6.2. in patients concurrently using recreational or medicinal cannabis or other cannabinoid-based medications. | There is limited 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 used recreational or medicinal cannabis in the past or cannabinoid-based medications within the 3 months before 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.<br>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 = antiseizure medication; CI = confidence interval; ICER = incremental cost-effectiveness ratio; ILAE = International League Against Epilepsy; mTOR = mammalian target of rapamycin; QALY = quality-adjusted life-year; 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 a debilitating neurologic condition characterized by seizures and neuropsychiatric disorders (i.e., TSC-associated neuropsychiatric disorders [TANDs]), such as intellectual disabilities and behavioural disorders. CDEC acknowledged the importance

of reducing seizure frequency on overall QoL; even with many currently available ASMs, patients continue to have 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 = 56.9; range, 7.7 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 pretreated 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%). Because the 95% CI of the primary end point contained the potential for no clinical benefit, and the estimated absolute placebo-adjusted reduction (22.1%; 95% CI, not reported) was less than 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 Grading of Recommendations Assessment, Development and Evaluation (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 end point 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 the placebo group (36.0% versus 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 frequency of status epilepticus because of 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 because 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 other 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. In addition, no

outcomes related to behaviour or cognition were evaluated in the CARE6 trial. CDEC also 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. The lower (10 mg/kg/day) and higher (50 mg/kg/day) dosages were not considered for TSC-associated seizures because these doses are not approved by Health Canada, although CDEC acknowledged the potential for differences in dosing.
- At the time of the CARE6 trial, patients receiving mammalian target of rapamycin (mTOR) inhibitors (e.g., everolimus, sirolimus) were excluded. CDEC discussed that the antitumoral effect of mTOR inhibitors may result in decreased seizure frequency or severity, and there are challenges associated with determining the treatment benefit of cannabidiol if it is used concomitantly. In addition, 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 limitations of the open-label extension study, including the lack of comparator and that the population consisted of patients who completed the CARE6 double-blind period, which limits 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 because of 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. Although Canadian-specific estimates are lacking, TSC is estimated to occur in 1 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 neurologic manifestation of the disease, affecting upwards of 70% of patients. Seizures 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, resulting from 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.

TSC-associated seizures generally begin within the first year of life in most patients (62.5% to 73.0%) as infantile spasms characterized by sudden and brief extension or flexion of the extremities. Other seizure types associated with TSC include focal seizures, which occur in approximately two-thirds of patients who present with variable symptoms. These 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 can become refractory in two-thirds of patients.

Seizure burden in patients with TSC can be high; patients not receiving treatment report 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. TSC is a chronic, lifelong condition. Although the prognosis for many people living with TSC has improved in recent years and life expectancy has increased, careful monitoring of all organ systems and development is critical. Most patients require multidisciplinary care at tertiary institutions as a result of their seizures and/or aspects of TAND.

TSC 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 5 mm 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. Without genetic confirmation, patients are considered to who have TSC if they have 2 major diagnostic features or 1 major feature and 2 minor diagnostic features. Possible TSC is considered in patients with either 1 major diagnostic feature or 2 or more minor diagnostic features. Two genes have been identified that can cause TSC: *TSC1* and *TSC2*. Only 1 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 treatment strategy; antiepileptic drugs are the mainstay of current pharmacological treatment, consisting of sodium valproate, vigabatrin, levetiracetam, clobazam, lamotrigine, lacosamide, oxcarbazepine, topiramate, and carbamazepine in Canada. Additional nonpharmacological treatments for seizures related to TSC include a ketogenic diet, surgery for tumour removal, and vagus nerve stimulation.

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 aged 2 years and older.

The antiseizure mechanism of cannabidiol is unknown, although 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 signalling 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 1 week, the dosage should be increased to 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, the dosage can be increased up to a maximum recommended dosage 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 CEA and TSCST. The CEA collected input from its 24 member associations on the 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 that was conducted in September 2023.

Both patient groups emphasized the catastrophic nature of uncontrolled seizures in infants and children, which are linked to cognitive delays and physical disabilities and have a high correlation with 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 find 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. Caregivers are also exposed to the sometimes highly unpleasant side effects, including mood

swings, suicidal thoughts, memory loss, problems with concentration, fatigue, exhaustion, depression, and sexual dysfunction, 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, and headaches, among others. Both patient groups also highlighted the physical and emotional wellbeing of both caregivers and patients, the 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

Because 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 in 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, topiramate, levetiracetam, brivaracetam). Treatments targeting the mTOR pathway, such as everolimus and sirolimus, are used to treat some tumours associated with TSC; however, there is controversy about whether they improve seizure frequency and neuropsychiatric comorbidities. In addition, 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 tumour 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 have 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 behaviour and may require constant monitoring.

The clinical experts noted that patients with TSC-associated seizures who are most in need of intervention would be those whose seizures remain uncontrolled by their current therapies or those who have behavioural issues on their current treatments. The experts considered that the patients who would be most likely to benefit from cannabidiol are those with intellectual disabilities and developmental delays. Patients with neuropsychiatric comorbidities could also benefit from cannabidiol because it may improve neuropsychiatric symptoms, whereas other available ASMs may worsen these symptoms. The experts also noted that eligible

patients would be easily identifiable by clinicians based on the patients' number and type of seizures as well as comorbidities. The clinical experts emphasized that caution and monitoring should be taken in treating patients with a history of depression or with liver disease, particularly for patients taking concomitant valproate. Dose adjustment may be required in patients who are taking concomitant clobazam and mTOR inhibitors because of the increased levels of desmethylclobazam and mTOR due to the administration of cannabidiol. In addition, the safety of cannabidiol in pregnancy has not been established, 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, although important, QoL measurements, caregiver burden, increase in independence, and clinical global impression are not commonly used in clinical practice, although 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, although patients are usually 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 (SAEs), such as elevation of liver enzymes of more than 5 times the limit, severe sedation, nausea, and allergic reaction. 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 because rescue medication 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., | CDEC and the clinical experts noted that although everolimus has Health Canada approval as adjunctive |

| Drug program implementation questions | Response |
|---|---|
| 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.<br>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? | treatment of seizures associated with TSC in patients aged 2 years and older, the primary indication and use of this therapy is as a chemotherapy for tumour shrinkage, which 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, although genetic testing was not a requirement in the CARE6 trial to diagnose TSC.<br>Pathogenic variants of *TSC1* and *TSC2* provide a definite diagnosis in 85% to 90% of patients.<br>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 and MRI).<br>Although genetic testing is widely available, some families choose not to proceed with genetic testing for personal, ethical, or other reasons. 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 1 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 ASMs before enrolment.<br>Oxcarbazepine has a higher threshold of initiation of coverage, requiring 1 to 3 ASMs to have failed.<br>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.<br>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 because this could be high for some patients who are less refractory. Although 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-associated epilepsy, and successful therapy is determined by a reduction in seizure frequency.<br>What objective measures are used in routine clinical practice to assess therapeutic response in patients with TSC-associated seizures? | 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.<br>Quality of life of patients is another metric that is considered by treating physicians. However, no specific QoL tools are generally used in practice; rather, patients and caregivers provide their own overall assessment of how their QoL has changed (e.g., increase or decrease in seizure frequency and severity, increased alertness). |

| Drug program implementation questions | Response |
|---|---|
| **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 (25 mg/kg/day and 50 mg/kg/day) was not reflective of the dosing criteria for TSC (10 mg/kg/day to 25 mg/kg/day) in the product monograph.<br>There is potential for prescribers to increase the dose to those used in the clinical trials, impacting cost.<br>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; the clinical experts also noted this was 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 a dosage of cannabidiol beyond the indicated dosage would be prescribed. If prescribed, 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.<br>Patients are required to see a specialist to be prescribed treatment for TSC-associated seizures, although administration of treatment is not a concern and does not need to be done in specialized centres. Recently, virtual care has become more common and should assist with treatment monitoring. |
| Cannabidiol is available as an amber liquid with 100 mg/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.<br>More information about drug interactions would be beneficial. | No response required. For CDEC consideration. |
| **Generalizability** | |
| The CARE6 trial was a multisite, 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.<br>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. |
| 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 | Most patients with TSC-associated seizures who use medical cannabis incur significant out-of-pocket costs because it is not generally covered by most plans. As such, |

| Drug program implementation questions | Response |
|---|---|
| product availability and quality, pharmacist involvement and medication review, and coverage by public and private insurers [currently only VAC and some private insurers cover medical cannabis products]).<br>Are there any challenges related to using the medical cannabis pathway supported by Health Canada?<br>Do you foresee other patients with drug-resistant epilepsy wanting access to Epidiolex? | 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 and caregivers may be interested in switching to cannabidiol because it is a "natural" product, although 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 diarrhea, 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 patients who received cannabidiol 25 mg/kg/day compared to 8.4% of patients in the placebo group.<br>How significant are the side effects for cannabidiol when compared to alternative ASMs?<br>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 would not prompt discontinuation of treatment.<br>CDEC and the clinical experts noted that there is a concern about the impact of cannabidiol on the developing brain. The mechanism and impact of this is not fully understood, so patients would be carefully monitored. In addition, 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 50 mg/kg/day.<br>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 3-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 = antiseizure medication; BIA = budget impact analysis; CDEC = Canadian Drug Expert Committee; GI = gastrointestinal; mTOR = mammalian target of rapamycin; TSC = tuberous sclerosis complex.

# Clinical Evidence

## Systematic Review

### Description of Studies

One phase III, placebo-controlled RCT (CARE6; N = 224) evaluated the reduction in seizure frequency using cannabidiol oral solution versus placebo as adjunctive therapy for the treatment of seizures in children and adults with TSC whose seizures were 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 was not included in this report because it is not a recommended dosage per Health Canada. 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. Mean age was 13.7 years (25 mg/kg/day: mean = 14.1 years; placebo: mean = 13.9 years); there were some baseline imbalances that were compatible with chance. All patients had TSC-associated seizures, with type 2 focal seizures occurring most frequently in patients in both groups (25 mg/kg/day: n = 46 [61.3%]; pooled placebo: n = 50 [65.8%]), followed by type 1 focal motor seizures (25 mg/kg/day: n = 29 [38.7%]; placebo: n = 33 [43.4%]). The mean number of TSC-associated seizures during the baseline period of 28 days 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 previously taken ASMs was 4 (range, 0 to 15).

### Efficacy Results

#### *Percent Change From Baseline in Seizure Frequency*

The primary end point of the CARE6 trial was the change from baseline in the number of TSC-associated seizures during the treatment period. The mean percentage reduction from baseline for the cannabidiol 25 mg/kg/day group was 48.6% (95% CI, 40.4% to 55.8%) and 26.5% (95% CI, 14.9% to 36.5%) for the placebo group. The relative treatment ratio of cannabidiol to placebo from the negative binomial regression analysis 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, although the reductions in seizure frequency observed in patients who were also taking clobazam appeared larger than in those who were not taking clobazam (the 95% CIs overlapped).

#### *Proportion of Patients With 25% or More Reduction in Seizure Frequency, 50% or More Reduction in Seizure Frequency, and Total Seizure Freedom*

The proportion of patients who had a 50% or more reduction from baseline in TSC-associated seizure frequency was the first key secondary end point of the CARE6 trial. In the double-blind treatment period, 27 patients (36.0%) in the cannabidiol 25 mg/kg/day group and 17 patients (22.4%) in the pooled placebo group

experienced a 50% or more reduction in seizure frequency (OR = 1.95; 95% CI, 0.95 to 4.00; P = 0.0692). The difference in the proportion of patients who had a 50% or greater reduction in TSC-associated seizure frequency between the cannabidiol 25 mg/kg/day group compared to the pooled placebo group was 13.6% (95% CI, −0.7% to 28.0%).

The proportion of patients who had a reduction in TSC-associated seizure frequency of at least 25% and the proportion who had seizure freedom (100% reduction in seizure frequency) were secondary end points of the CARE6 trial. During the treatment period, 43 patients (57.3%) and 33 patients (43.4%) in the cannabidiol 25 mg/kg/day and placebo groups, respectively, experienced a 25% or greater reduction in seizure frequency (OR = 1.75; 95% CI, 0.92 to 3.33). The difference in the proportion of patients who achieved a 25% or greater reduction in TSC-associated seizure frequency between the cannabidiol 25 mg/kg/day and placebo groups 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*

HRQoL was assessed using the Quality of Life in Childhood Epilepsy (QOLCE) questionnaire in pediatric patients aged 2 to 18 years and the Quality of Life in Epilepsy (QOLIE)-31-P questionnaire 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 and 42 patients at the end of treatment. For the placebo group, 50 patients had an overall QOLCE QoL score at baseline and 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 points) and 1.6 points (95% CI, −1.8 to 4.9 points) 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 by 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 points) and 2.3 points (95% CI, −15.0 to 19.7 points) 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 mean number of days of rescue medication use in the cannabidiol 25 mg/kg/day group and placebo group was 2.14 days (SD = 2.19 days) and 2.32 (SD = 3.20 days), respectively. The mean number of days of rescue medication use during the treatment period was 0.79 days (SD = 2.47 days) in the cannabidiol 25 mg/kg/day group and 0.55 days (SD = 1.40 days) in the placebo group, representing a mean change from baseline of 0.19 days (SD = 2.84 days) and −0.92 days (SD = 1.86 days), respectively. The

mean difference in reduction from baseline in rescue medication use days between the cannabidiol 25 mg/kg/day group and the placebo group was 0.96 days (95% CI, −0.65 to 2.56 days).

*Status Epilepticus*

During the baseline period, no patients in the cannabidiol 25 mg/kg/day group had status epilepticus compared to 3 patients (3.9%) in the placebo group. 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 Behavior 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 points (SD = 22.24 points) and 51.5 points (SD = 25.57 points), respectively, representing a LS mean change from baseline of −0.0 points (95% CI, −1.6 to 1.5 points) for cannabidiol 25 mg/kg/day, and −0.0 points (95% CI, −1.6 to 1.5 points) 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 patients (93.3%) in the cannabidiol 25 mg/kg/day group and by 72 patients (94.7%) 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 (12; 16.0%), alanine aminotransferase (ALT) (9; 12.0%), and aspartate aminotransferase (AST) (8; 10.7%); 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 patients (12.5%) in the CARE6 trial experienced a total of 44 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%), and status epilepticus, vomiting, and viral gastroenteritis (2; 2.7% each). Serious AEs in the placebo group only occurred in 2 patients (2.6%) and included pneumonia and status epilepticus (1; 1.3% each).

A total of 20 patients (8.9%) 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 patient (1.3%). The 2 patients in the placebo group discontinued treatment due to TEAEs of ataxia (1 patient) and agitation (1 patient).

There were no deaths reported during the CARE6 trial.

### *Notable Harms*

AEs of special interest to this review were hepatocellular injury and hypersensitivity reactions. In the cannabidiol 25 mg/kg/day group, 1 patient (1.3%) had liver injury and 1 patient (1.3%) had a type IV hypersensitivity reaction. These 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. Because of the known interaction between clobazam and cannabidiol, failure to stratify by clobazam use was a limitation; however, 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% versus 1.3%), primarily due to AEs (10.7% versus 0.0%). Although the CARE6 trial was 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. Based on discussion with the clinical experts consulted by CADTH, subgroups of interest to this review included clobazam use and the number of concurrent and prior ASMs. Results generally supported the primary analysis, although they were not statistically powered to detect within-group or between-group differences. In addition, 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 end points of CARE6. The QOLCE and QOLIE-31-P were considered reliable and valid measures for epilepsy in TSC, although 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. Rescue medication usage was not accounted for in the primary or key secondary end point 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, the maximum recommended Health Canada–approved dosage of cannabidiol for TSC-associated seizures is 12.5 mg/kg twice daily (25 mg/kg/day), so the cannabidiol 50 mg/kg/day dose was not of interest to this review.

The CARE6 trial was an international multicenter study, but 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 28-day baseline seizure frequency (range, 8 to 558 days) and the number of prior (range, 0 to 15) and concurrent (range, 0 to 5) ASMs. 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. In addition, there was heterogeneity in the concomitant ASMs received by patients in the CARE6 trial. 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. An additional consideration as noted by patient groups and the clinical experts consulted by CADTH is 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, because the effects 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, 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 the RCT started as high-certainty evidence and it 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 the 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 who responded to treatment (i.e., achieving target reductions of 25% or 50% more) or had 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 who had episodes of status epilepticus at week 16, the change from baseline in rescue medication use days at week 16, the change from baseline in Vineland II Adaptive Behavior Scale at week 16, the proportion of patients with at least 1 SAE, and the 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 who had episodes of status epilepticus, and changes from baseline in rescue medication use.

### *Results of GRADE Assessments*

Table 3 presents the GRADE summary of findings for cannabidiol versus placebo for outcomes in the pivotal CARE6 trial.

## Table 3: Summary of Findings for Epidiolex Versus Placebo as 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<br>Follow-up: 113 days | 151 (1 RCT) | Ratio: 0.699 (0.57 to 0.86)<br>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 compared with placebo. |
| Percentage of patients with ≥ 50% reductions in TSC-associated seizure frequency<br>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 with a 50% reduction in TSC-associated seizure frequency compared with placebo. The clinical importance of the reduction is unclear. |
| Percentage of patients with ≥ 25% reductions in TSC-associated seizure frequency<br>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 with a 25% reduction in TSC-associated seizure frequency compared with placebo. The clinical importance of the reduction is unclear. |
| Percentage of patients with seizure freedom (100% reduction in TSC-associated seizure frequency)<br>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 with total TSC-associated seizure freedom (100% reduction in seizure frequency) compared with 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 | | |
| **Status epilepticus and need for rescue medication** | | | | | | | |
| Proportion of patients with episodes of status epilepticus<br>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 episodes of status epilepticus compared with placebo. The clinical importance of the effect is uncertain. |
| Mean change from baseline in rescue medication use days (per 28 days)<br>Follow-up: 113 days | 151 (1 RCT) | NA | −0.92 (SD = 1.86) | 0.19 (SD = 2.84) | 0.96 (−0.65 to 2.56) | Low[c,d] | Cannabidiol may result in little to no difference in rescue medication use compared with placebo. The clinical importance of the effect is uncertain. |
| **Quality of life and adaptive behaviour** | | | | | | | |
| Change from baseline in QOLCE overall QoL score (points)<br>Follow-up: 113 days | 82 (1 RCT) | NA | 1.6 (−1.8 to 4.9) | 3.1 (−0.6 to 6.7) | 1.5 (−3.3 to 6.3) | Very low[c,e] | The effect of cannabidiol on the QOLCE overall QoL score compared with placebo is very uncertain. |
| Change from baseline in QOLIE total score (points)<br>Follow-up: 113 Days | 22 (1 RCT) | NA | 2.3 (−15.0 to 19.7) | −1.4 (−16.2 to 13.5) | −3.7 (−16.6 to 9.2) | Very low[c,f] | The effect of cannabidiol on the QOLIE total score compared with placebo is very uncertain. |
| Change from baseline in Vineland II Adaptive Behavior Scale composite score (points)<br>Follow-up: 113 days | 90 (1 RCT) | NA | 0.0 (−1.6 to 1.5) | 0.0 (−1.6 to 1.5) | 0.0 (−2.2 to 2.1) | Very low[c,g] | The effect of cannabidiol on the Vineland II Adaptive Behavior Scale composite score compared with placebo is very uncertain. |

| Outcome and follow-up | Patients (studies), N | Relative effect (95% CI) | Absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|---|
| | | | Placebo | Cannabidiol | Difference | | |
| **Harms**[h] | | | | | | | |
| Hepatocellular injury (safety end point)<br>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 compared with placebo. The clinical importance of the effect is uncertain. |
| SAEs<br>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 compared with 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 an approximately 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. Although 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 minimally important difference (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 AE 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 the CARE6 study.

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

Patients experienced a reduction in overall QOLIE-31-P (patient aged ≥ 19 years) total score relative to the prerandomization baseline of the double-blind phase, with a mean change from baseline of −9.0 points (SD = 17.99 points) for all evaluable patients (n = 9 of 199) and −7.4 points (SD = 18.57 points) for patients aged 19 years or older (n = 8) at OLE end of treatment. Based on a change from the double-blind phase baseline to OLE end of treatment, a reduction in the mean QOLIE-31-P total score was observed in the cannabidiol cohort (−14.8 points; SD = 20.60 points; n = 5) and the placebo cohort (−1.8 points; SD = 13.2 points; n = 4). For patients aged 19 years and older (n = 8), mean QOLIE-31-P total score reduction was −13.1 points (SD = 23.39 points; n = 4) in cannabidiol cohort versus −1.8 points (SD = 13.12 points; n = 4) in the placebo cohort.

Based on change from the double-blind baseline to OLE end of treatment, a reduction in mean number of days of rescue medication use was −0.44 days (SD = 4.09 days) in the total population (n = 55 of 199): −0.10 days (SD = 4.73 days) in the cannabidiol cohort (n = 35 of 124) and −1.02 days (SD = 2.64 days) in placebo cohort (n = 20 of 75).

The number of patients with episodes of 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 versus placebo during the double-blind phase of the CARE6 study.

### Harms Results

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

There were 18 patients (9%) 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, although this 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. The open-label design may also bias the reporting of subjective end points, including AEs, SAEs, and TEAEs. Because 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 who were more tolerant of cannabidiol, which can lead to a selection bias because patients who do not respond 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 the 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 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, but there were no study sites in Canada. No evidence indicating a difference between the study population and patients in Canada was identified in consultation with the clinical experts. The median number of dosing days was 369.5 days (range, 95.0 to 1,462 days) which provides longer follow-up for AE assessment versus the double-blind phase of the CARE6 study; however, the proportion of patients who adhered to cannabidiol during the longer follow-up was not reported. Thus, the study drug exposure among patients in the OLE study was uncertain. Approximately half the 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 patients 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 4: Summary of Economic Evaluation

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost-utility analysis<br>Markov model |
| **Target population** | Patients 2 years of age and older with TSC and a history of epilepsy that is inadequately controlled by their current ASM (i.e., patients who experience at least 8 seizures during a 28-day baseline period). |
| **Treatment** | Cannabidiol in combination with usual care.<br>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 older than 18 years is $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, life-years |
| **Time horizon** | Lifetime (100 years) |
| **Key data source** | CARE6: phase III, randomized, double-blind, placebo-controlled trial (data cut-off: February 26, 2019) |
| **Key limitations** | • The submitted model does not reflect the full Health Canada–indicated population for TSC. Effectiveness of cannabidiol plus 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 including patients with fewer than 8 seizures per 28 days is unknown.<br>• 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 HRQoL associated with a seizure day.<br>• 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 plus usual care were accrued by caregivers, not patients with TSC.<br>• The long-term relative effectiveness of cannabidiol plus usual care compared to usual care alone is highly uncertain. Approximately 97% of the incremental benefit associated with cannabidiol was accrued after the trial period.<br>• 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. |

| Component | Description |
|---|---|
| **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.<br>• In the CADTH base case, cannabidiol plus 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 plus usual care to be cost-effective compared to usual care alone at a willingness-to-pay threshold of $50,000 per QALY gained.<br>• The cost-effectiveness of cannabidiol plus 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 plus usual care decreased to $169,662 per QALY gained (incremental costs: $278,484; incremental QALYs: 1.64) relative to usual care. |

ASM = antiseizure medication; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; 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 Non-Insured Health Benefits (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 budget impact analysis 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 plus 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

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