CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

cannabidiol (Epidiolex)

(Jazz Pharmaceuticals Canada, Inc.)

Indication: Epidiolex is indicated as adjunctive therapy with other anti-seizure medications for the treatment of seizures associated with Tuberous Sclerosis Complex (TSC) in patients 2 years of age and older.

April 8, 2024

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	
Brand name (generic)	Cannabidiol (Epidiolex)
Indication(s)	As adjunctive therapy for the treatment of seizures associated with Tuberous Sclerosis Complex (TSC) in patients 2 years of age and older
Organization	Tuberous Sclerosis Canada Sclérose Tubéreuse (TSCST)
Contact information[a]	Name: Cathy Evanochko

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale. We are very pleased to have access to an anti-seizure medication that has proven very effective on seizures caused by TSC.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☒
If not, what aspects are missing from the draft recommendation? We feel that some of the reimbursement conditions are unreasonable and not adequately supported by the reasons and/or implementation guidelines. Please see condition comments below.		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. We feel that the reasons and/or implementation guidance don't always support the recommendations. Please see condition comments below.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification. Reimbursement Conditions on pages 4 and 5: 1. We fully support this condition, reason and guidance.		

2. This reimbursement condition is unacceptable. 2.1 states that this medication can be used if patients have at least 8 seizures per 28 days prior to initiating cannabidiol. We agree with 2.2 that cannabidiol should be considered when patients have inadequately controlled seizures. However, limiting access only to patients who have at least 8 seizures in 28 days will create a situation of inequitable access to the medication. A patient could have 1 catastrophic seizure that would benefit from treatment with this medication. Additionally, it is difficult to measure seizures caused by TSC as patients can have many different types of seizures, sometimes in a cluster, so very hard to count. We ask that condition 2.1 be removed, and 2.2 kept.
3. We support this recommendation and guidance, but not necessarily the reason. We agree that patients should be monitored every 6 months for the first year or 2, but after that annually is much easier for families to manage.
4. We agree with the recommendations and reasons stated around when cannabidiol should be discontinued.
5. We agree that ideally patients should be under the care of a neurologist. However, patients do not always have access to a neurologist. Patients are often managed by their family doctor, especially patients who live in rural settings. We ask that the word “must” be changed to “should”.
6. Condition 6.1 is too restrictive. Yes, there can be interaction between mTor inhibitors and cannabidiol, however, this does not mean patients cannot use both medications. Barring patients who are taking an mTor inhibitor results in unreasonable access restrictions. mTor inhibitors are the first line of treatment for those who have AMLs in their kidneys or a SEGA (brain). This should not prevent patients from having access to cannabidiol. There are many, many medications that interact with each other, but are managed by monitoring blood levels, lower doses, etc. We ask that condition 6.1 be removed. We totally agree with condition 6.2.
7. Cannot comment
8. Cannot comment

We hope that a price acceptable to the recommendation of Epidiolex be reached so patients have access to this effective medication in the treatment of seizures caused by TSC.

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*Cathy Evnochko*
Position	*Board Chair*
Date	*26-03-2024)*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0798
Brand name (generic)	Cannabidiol
Indication(s)	Tuberous Sclerosis Complex
Organization	Canadian League Against Epilepsy (CLAE)
Contact information[a]	Juan Pablo Appendino (in representation of CLAE)

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

The CLAE would like CADTH to reconsider the following condition/s:

- #2.1: At least 8 seizures per 28 days prior to initiation of cannabidiol.

CLAE believes that patients with TSC could have drug-resistant epilepsy; although a low monthly seizure burden of <8 seizures/28 days could be present but still benefit from the anti-seizure effects of Epidiolex (cannabidiol). We believe that a seizure count of 1 motor seizure (or a non-motor that is easy to determine as seizure) per month should be considered for cannabidiol therapy. The rationality behind this statement is that uncontrolled seizures can have a devastating impact on quality of life and overall functioning in TSC (Skrobanski et al, 2023, *Pharmacoecon Open*; 7(2):299-312), disregarding of the number of seizures but rather being the epilepsy active or not as the presence of active epilepsy reduces the QOLIE-31 score by 12.6 points (p=<0.001. Zöllner JP, et al, 2021, *Neurol Res Pract;* 3(1):35). Furthermore, for patients that have lower seizure counts per month, even having one or two bilateral monthly tonic-clonic seizures can increase the risk of sudden unexpected death in epilepsy (SUDEP) (Sveinsson et al, 2020, *Neurology*; 98(4): e419-e429). The arbitrary cut-off of 8 seizures in 28 days, based on the clinical trial design where mostly severe and devastated patients with TSC were included, is not reflective of every-day clinical practice where a large degree of differing monthly seizure frequency is seen on a month-to-month basis. In addition, it might be difficult (and not accurate, at times) for families to keep track of how many seizures happen, and some types of seizures might not be even noticed because they can be subtle in TSC. (Lynch et al, 2023, *Epilepsia*; 64(4):386-395). Therefore, CLAE's opinion is that Epidiolex could be prescribed and should be covered by insurance in patients with TSC and drug-resistant epilepsy even if the monthly seizure rate is of a single monthly seizure (active epilepsy). CLAE understands and agrees that patients must have drug-resistant epilepsy and should have tried at least two anti-seizure medications prior to the use of cannabidiol (Epidiolex)

- #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.

CLAE believes that patients who are on mTOR inhibitor should not be prevented from accessing cannabidiol. CLAE knows there is a drug interaction between MTOR inhibitor and cannabidiol; however, this can be managed clinically and with laboratory investigations looking at levels of mTOR-inhibitors in the blood. In addition, the titration of cannabidiol could be decelerated, and these patients can be under clinical observation to prevent toxicity. The FDA does not prohibit patients undergoing mTOR therapy from initiating cannabidiol but advises clinical monitoring of drug levels. We argue that the exclusion of patients undergoing mTOR therapy for managing the manifestations of TSC (such as SEGAs, AMLs, LAM) would unjustifiably impede numerous patients with refractory TSC from obtaining cannabidiol treatment. Real-life experience exists and shows it can safely be used (Tzadok M, et al. *Pediatr Neurol*. 2024 150:91-96.)

CLAE supports the concept of remaining on other cannabinoids/CBD products prior to starting cannabidiol and during their transition from a less purified medical cannabis product to Epidiolex as we believe that the recommendation #6.2 is prohibitive for patients who are currently on other CBD products and would like to switch to cannabidiol. A "wash out" period could be very dangerous in some cases (responders to CBD) as it can bring seizure increase with higher chances of injuries or even SUDEP. A gradual transition could/should be considered without the need of a "wash out" period.

- #7: 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.

CLAE would strongly recommend retaining the recommendation #7 of implementing "A reduction in price". As you well stated, a price reduction of at least 60-65% is required. A price comparison of a similar product may help to guide the pharmaceutical company on what we are looking for (i.e. RHO Phyto is $0.027/mg [https://mymedi.ca/products/rho-phyto-micro-drop-100-cbd-cannabis-oil/]; Tilray 2:100 is $0.1/mg [https://www.tilraymedical.ca/products/105]). Bravo for your recommendation!

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
Yes, these are clearly stated.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
See Rationale in Question 3.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☐
	Yes	☒
Discussed with Ontario TSC Network.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr. Juan Pablo Appendino*
Position	*Pediatric Neurologist, Alberta Children's Hospital. Leader of the Medical and Therapeutics Committee CLAE.*
Date	*28-03-2024*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Jazz Pharmaceuticals	☒	☐	☐	☐
UCB Pharmaceuticals	☐	☐	☒	☐
Takeda Pharmaceutical	☒	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0798
Brand name (generic)	Cannabidiol
Indication(s)	Tuberous Sclerosis Complex
Organization	Ontario TSC Network
Contact information[a]	Name: Dr. Robyn Whitney and Dr. Katie Muir

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

The stakeholder does not agree with the condition regarding that a patient must have at least eight seizures in the last 28 days in order to qualify for cannabidiol. The stakeholder believes that patients with TSC who have refractory epilepsy, but lower seizure counts per month should also be considered for cannabidiol therapy, given the burden that uncontrolled seizures can have on quality of life and overall functioning in TSC (Skrobanski et al, 2023, *Pharmacoecon Open*; 7(2):299-312). Furthermore, the criteria for eight seizures in 28 days is based on clinical trial design and is not reflective of every day clinical practice. Furthermore, it may not be practical for families to provide such seizure counts and some seizure types may go unrecognized as subtle seizures can occur in TSC (Lynch et al, 2023, *Epilepsia*; 64(4):386-395). Furthermore, for patients that have lower seizure counts per month, even having one or two bilateral tonic-clonic seizures on a monthly basis can increase the risk of sudden unexpected death in epilepsy (SUDEP) (Sveinsson et al, 2020, *Neurology*; 98(4): e419-e429). Therefore, it is the stakeholder's opinion that individuals with refractory epilepsy and TSC and lower seizure counts (i.e., <8 seizures per month) should be considered for cannabidiol therapy. The stakeholder agrees that patients must have refractory epilepsy and should have tried at least two ASMS prior to the use of cannabidiol.

The stakeholder also does not agree with the recommendation that patients must be off other CBD products prior to starting cannabidiol. This recommendation is prohibitive for patients who are currently on other CBD products and would like to switch to cannabidiol. Weaning off other CBD products rather than directly switching to cannabidiol may result in an increased seizure burden.

The stakeholder does not agree that patients who are on mTOR inhibitor should be prevented from accessing cannabidiol. The stakeholder understands there is a drug interaction between MTOR inhibitor and cannabidiol, however, this can be managed clinically and levels of mTOR can be measured in the blood. Furthermore, the titration of cannabidiol could be slowed and these patients can be monitored on a clinical basis to ensure toxicity does not occur. The FDA does not preclude

patients who are on mTOR from starting cannabidiol, however recommends clinical monitoring of drug levels. We believe that excluding patients who are on mTOR therapy for treatment of the manifestations of TSC (i.e., SEGAs, AMLs, LAM) will unnecessarily prevent many patients with refractory TSC from accessing cannabidiol.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
Yes, these are clearly stated.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
See Rationale in Question 3.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

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- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
No		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr. Robyn Whitney*
Position	*Pediatric Neurologist, Ontario TSC Network*
Date	*25-03-2024*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.	

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Jazz Pharmaceuticals	☐	☐	☒	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Dr. Katie Muir*
Position	*Pediatric Neurologist, Ontario TSC Network*
Date	*25-03-2024*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Jazz Pharmaceuticals	☐	☐	☒	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0798
Name of the drug and Indication(s)	Cannabidiol (Epidiolex) as adjunctive therapy for the treatment of seizures associated with Tuberous Sclerosis Complex (TSC) in patients 2 years of age and older
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☐
	No requested revisions	X

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0798-000
Brand name (generic)	EPIDIOLEX (cannabidiol)
Indication(s)	The adjunctive therapy with other anti-seizure medications for the treatment of seizures associated with TSC in patients two years of age and older
Organization	Jazz Pharmaceuticals Canada
Contact information[a]	[redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
No comment.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
No comment.		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒

Page 23, Budget Impact, paragraph 2: "CADTH conducted reanalyses of the BIA by … adopting a maintenance dose of 23 mg/kg/day among patients treated with cannabidiol; and using 100% adherence in the calculation of drug costs."

It is Jazz's position that the dosing assumptions in the submitted budget impact model, and the associated annual drug costs, are reflective of the dose of EPIDIOLEX that would be taken by patients in clinical practice, based on the Health Canada Product Monograph[1] and real-world dosing evidence.[2] CADTH's reanalyses represent close to the maximum dose allowed by the product monograph and therefore the maximum annual drug costs possible for EPIDIOLEX, not what would be expected in clinical practice.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
No comment.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

Page 5, reimbursement condition 6: "6. Cannabidiol should not be reimbursed when given in the following instances: 6.1. In patients concurrently using mTOR inhibitors"

Jazz disagrees with the restriction of reimbursement of EPIDIOLEX for patients with tuberous sclerosis complex (TSC) concurrently using mammalian target of rapamycin (mTOR) inhibitors.

Although it is expected that the number of patients concurrently using cannabidiol and mTOR inhibitors (such as everolimus) will be low to moderate, if this restriction is applied, those patients will be unfairly denied the opportunity of a novel treatment for their seizures that is available to other patients with TSC-associated seizures who are not taking mTOR inhibitors.

- There are some circumstances where physicians may wish to use an mTOR inhibitor and cannabidiol in combination. Everolimus has separate indications for the treatment of Subependymal Giant Cell Astrocytomas (SEGAs) and renal angiomyolipomas, which are not related to the treatment of seizures. In these patients, everolimus is being used as a chemotherapy agent, whereas cannabidiol is an anti-seizure medication (ASM).
- In the CADTH Clinical Review report, the Canadian clinical experts consulted were clear that the use of mTOR inhibitors in TSC is mostly as a chemotherapy to shrink tumors, and that interruption of their use can lead to seizure worsening:
    - "Treatments targeting the mTOR pathway such as everolimus and sirolimus are used to treat some of the tumors associated with TSC, however, there is controversy about whether they improve seizure frequency and neuropsychiatric comorbidities … 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."[3]
- The Canadian clinical experts also consulted mentioned dose adjustments with concomitant mTOR inhibitors and cannabidiol, indicating that they had assumed that some patients would be taking the drugs together:
    - "Additionally, dose adjustment may be required in patients who are taking concomitant … mTOR inhibitors due to … increased mTOR levels due to the administration of cannabidiol."[3]
- These dose adjustments are also mentioned in the Canadian Product Monograph for Epidiolex (Table 10),[1] which includes recommendations for dose adjustments if cannabidiol and everolimus are to be used concurrently.
    - "When initiating Epidiolex in patients taking everolimus, monitor therapeutic drug levels of everolimus and adjust the dosage accordingly".
- The information above clearly indicates that there are patients with TSC for whom concurrent everolimus and cannabidiol would be the treatment of choice in order to manage both SEGAs or renal angiomyolipomas and seizures. Interruption of the use of mTOR inhibitors in order to start cannabidiol is not an option for these patients without risking brain tumor regrowth. In addition, the possibility of dose reductions in everolimus when used concurrently with cannabidiol may bring benefits in terms of reduced side-effects and/or reduced costs.

CADTH has suggested a reimbursement condition that cannabidiol should not be reimbursed in patients concurrently using mTOR inhibitors as there is "no evidence to support the use of cannabidiol in conjunction with mTOR inhibitors". However, there is evidence showing the use of cannabidiol in conjunction with mTOR inhibitors, including evidence from the GWPCARE6 randomised controlled trial (RCT) and open-label extension (OLE) study, as well as real-world evidence (RWE). This is outlined below:

- GWPCARE6 RCT: Although the use of mTOR inhibitors as ASMs was an exclusion criterion in the GWPCARE6 RCT, this criterion was included as mTOR inhibitors were not approved for treatment of patients with TSC at the time of the trial and use in these patients was only experimental at the time. However, despite patients being excluded from taking mTOR inhibitors as ASMs, there were 25 patients in the Safety Analysis Set who were taking

everolimus or sirolimus as immunosuppressants as concomitant medication (i.e., for reasons other than seizure reduction).[4]
- GWPCARE6 OLE: On-label use of mTOR inhibitors (for the treatment of seizures or tumors) was permitted in the OLE phase of the GWPCARE6 trial. In the OLE Safety Analysis Set, nine patients were taking everolimus. Eight patients were taking it as a concomitant ASM, and one further patient where it was listed in the trial tables as an 'Other Concomitant Medication'.[5]
- Real-world evidence from an Italian study in 12 patients with TSC concluded that a reduction in monthly seizures was observed during co-treatment with cannabidiol and everolimus, and that the combination was also shown to be safe and tolerable.[6]

The evidence above shows that mTOR inhibitors and cannabidiol have been used concomitantly in clinical trials and in real-world clinical practice. In patients with TSC-associated epilepsy taking the drugs concurrently, seizure reductions were observed, and no new safety concerns were reported.

Page 4, reimbursement condition 2: "2. Patients must have the following: 2.1. At least 8 seizures per 28 days prior to initiation of cannabidiol."

Jazz disagrees with restricting access to EPIDIOLEX to only patients who have at least eight seizures per 28 days prior to initiation.
- Although it is necessary in a clinical trial setting to establish minimum number of seizures during the baseline period, in clinical practice the decision to start patients on EPIDOLEX would be based on their lack of seizure control, not a specific number of seizures.
- Additionally, it is often difficult for patients with TSC, who experience a variety of development and neuropsychiatric symptoms, and/or caregivers to accurately track the number of seizures that a patient is experiencing.

It is Jazz's position that the initiation criteria for EPIDIOLEX should be based only on a patient having inadequately controlled seizures, and not a minimum number of seizures.

Page 5, reimbursement condition 5: "5. The patient must be under the care of a neurologist with experience in the diagnosis and management of TSC."

Jazz disagrees with restricting access to EPIDOLEX to only patients who are under the care of a neurologist. TSC is a multisystemic disorder which requires comprehensive management strategies. In practice, while neurologists play a pivotal role in overseeing the treatment of TSC, the nature of this syndrome often necessitates coordinated care involving multiple healthcare professionals. Given the multidisciplinary approach required for effective management of TSC, restricting prescription authority would be challenging as other specialists may be the primary point of care for the patient.
- ASMs that are indicated and funded for similar developmental and epileptic encephalopathies do not require patients to be under the care of a neurologist. For example, for rufinamide, which is indicated for patients with Lennox-Gastaut syndrome (LGS), CADTH recommended patients be under the care of a physician experienced in treating LGS,[7] and the Ontario Exceptional Access Program (EAP) criteria only requires that the patient is in the care of a physician experienced in managing seizures, not specifically a neurologist.[8] Similarly, for stiripentol, which is indicated for patients with Dravet syndrome, the Ontario EAP criteria requires that the request is submitted by a neurologist *or* pediatrician.[8]

It is Jazz's position that EPIDIOLEX should be prescribed by a physician with experience in the diagnosis and management of patients with TSC, not restricted specifically to neurologists.

[a] CADTH may contact this person if comments require clarification.

[1]GW Research Ltd (2023) (Product Monograph for EPIDIOLEX (cannabidiol)). November 15, 2023.
[2]Jazz Pharmaceuticals (2022). *VV-MED-29431 - Epidiolex Daily Dose in TSC - Patient INSIGHTS (INSIGHT Health) Germany*. Available online at: Accessed:
[3]Canadian Agency for Drugs and Technologies in Health (2024). *Draft Clinical Review Report: Cannabidiol (EPIDIOLEX)*. Available online at: Accessed: April 2024.
[4]GW Research Ltd. (2019, Data on File). *A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures.* (CSR GWEP1521). December 23, 2019.
[5]GW Research Ltd. (2021, Data on File). *A Double-blind, Randomized, Placebo-controlled Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P, CBD) as Add-on Therapy in Patients With Tuberous Sclerosis Complex who Experience Inadequately Controlled Seizures.* (CSR GWEP1521). November 24, 2021.
[6]Riva A, Davoli G, Roberti R, Amadori E, Moavero R et al. (2023) Cannabidiol plus everolimus for the treatment of TSC: real-world evidence. *International Epilepsy Congress*. Dublin, Ireland, September 2-6, 2023.
[7]Canadian Agency for Drugs and Technologies in Health (2012). *CDEC Final Recommendation: Rufinamide*. Available online at: https://www.cadth.ca/rufinamide. Accessed: April 2024.
[8]Ontario Ministry of Health (2023). *Exceptional Access Program Reimbursement Criteria for Frequently Requested Drugs*. Available online at: https://files.ontario.ca/moh-frequently-requested-drugs-en-2023-12-21.pdf. Accessed: April 2024.