

## CADTH REIMBURSEMENT REVIEW

# Stakeholder Feedback on Draft Recommendation

**cannabidiol (Epidiolex)**  
(Jazz Pharmaceuticals Canada, Inc.)

**Indication:** Epidiolex (cannabidiol) is indicated for use as adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) or Dravet Syndrome (DS) or Tuberous Sclerosis Complex (TSC) in patients one year of age and older.

April 8, 2024

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CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting stakeholder group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

# CADTH Reimbursement Review

## Feedback on Draft Recommendation

Stakeholder information		
CADTH project number	SR0800	
Brand name (generic)	Cannabidiol	
Indication(s)	Lennox-Gastaut	
Organization	Canadian League Against Epilepsy (CLAE)	
Contact information <sup>a</sup>	Juan Pablo Appendino (in representation of CLAE)	
Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	<input checked="" type="checkbox"/>
	No	<input type="checkbox"/>
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	<input checked="" type="checkbox"/>
	No	<input type="checkbox"/>
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	<input type="checkbox"/>
	No	<input checked="" type="checkbox"/>
<p>The CLAE would like CADTH to reconsider the following condition/s:</p> <ul style="list-style-type: none"> <li>- #2.1: At least 2 drop seizures per week over a 28-day period prior to initiation of cannabidiol.</li> </ul> <p>CLAE believes that patients with LGS could have drug-resistant epilepsy; although a low monthly seizure burden of &lt;2 drop 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 a seizure) per month should be considered enough to qualify for cannabidiol therapy, meanwhile they are drug-resistant (failure to 2 or more ASMs). The rationality behind this statement is that uncontrolled seizures can have a devastating impact on quality of life and overall functioning in LGS, although seizure-free days seems to have an even more positive impact on QoL (Auvin S, et al. <i>Epilepsy Behav.</i> 2021 Oct;123:108239. PMID: 34375802.). 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, <i>Neurology</i>; 98(4): e419-e429). The arbitrary cut-off of 2 drop-seizures in 28 days, based on the clinical trial design is not reflective of every-day clinical practice where a large degree of differing monthly seizure frequency is seen, changing month-to-month. Therefore, CLAE's opinion is that Epidiolex could be prescribed and should be covered by insurance in patients with LGS and drug-resistant epilepsy even if the monthly seizure rate is of a single monthly motor seizure.</p> <ul style="list-style-type: none"> <li>- #6: Cannabidiol should not be reimbursed in patients concurrently using cannabis products or other cannabinoid-based medications.</li> </ul> <p>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 is prohibitive for patients who are currently on other CBD</p>		

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 71% would be required for adjunctive cannabidiol to achieve an ICER of \$50,000 per QALY 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 70-75% 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!

<b>4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?</b>	Yes	<input checked="" type="checkbox"/>
	No	<input type="checkbox"/>
Yes, these are clearly stated.		
<b>5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?</b>	Yes	<input type="checkbox"/>
	No	<input checked="" type="checkbox"/>
See Rationale in Question 3.		

<sup>a</sup> 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	<input checked="" type="checkbox"/>
	Yes	<input type="checkbox"/>
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	<input checked="" type="checkbox"/>
	Yes	<input type="checkbox"/>
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	<input checked="" type="checkbox"/>
	Yes	<input type="checkbox"/>
If yes, please list the clinicians who contributed input and whose declarations have not changed:		
<ul style="list-style-type: none"> <li>Clinician 1</li> <li>Clinician 2</li> <li>Add additional (as required)</li> </ul>		

### 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
<input checked="" type="checkbox"/>	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
<i>Jazz Pharmaceuticals</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>UCB Pharmaceuticals</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<i>Takeda Pharmaceutical</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

New or Updated Declaration for Clinician 2	
<b>Name</b>	<i>Please state full name</i>
<b>Position</b>	<i>Please state currently held position</i>
<b>Date</b>	<i>Please add the date form was completed (DD-MM-YYYY)</i>
<input type="checkbox"/>	<b>I hereby certify</b> 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
<i>Add company name</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Add company name</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Add or remove rows as required</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

New or Updated Declaration for Clinician 3	
<b>Name</b>	<i>Please state full name</i>
<b>Position</b>	<i>Please state currently held position</i>
<b>Date</b>	<i>Please add the date form was completed (DD-MM-YYYY)</i>
<input type="checkbox"/>	<b>I hereby certify</b> 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
<i>Add company name</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Add company name</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Add or remove rows as required</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

# CADTH Reimbursement Review

## Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0800
Name of the drug and Indication(s)	Cannabidiol (Epidiolex) as adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome 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 <b>category</b> or patient <b>population</b> is requested	<input type="checkbox"/>
	Minor revisions: A change in reimbursement <b>conditions</b> is requested	<input type="checkbox"/>
No Request for Reconsideration	Editorial revisions: Clarifications in recommendation <b>text</b> are requested	<input type="checkbox"/>
	<b>Not requested revisions</b>	<input type="checkbox"/>

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
<b>a) Recommendation rationale</b>
Please provide details regarding the information that requires clarification.
<b>b) Reimbursement conditions and related reasons</b>
Please provide details regarding the information that requires clarification.
<b>c) Implementation guidance</b>
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 Reimbursement Review Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0800-000
Brand name (generic)	EPIDIOLEX (cannabidiol)
Indication(s)	As adjunctive therapy for seizures associated with LGS in patients two years of age and older
Organization	Jazz Pharmaceuticals Canada
Contact information <sup>a</sup>	<div style="background-color: black; width: 100px; height: 15px; margin-bottom: 5px;"></div> <div style="background-color: black; width: 250px; height: 15px; margin-bottom: 5px;"></div> <div style="background-color: black; width: 180px; height: 15px; margin-bottom: 5px;"></div> <div style="background-color: black; width: 60px; height: 15px;"></div>
Stakeholder agreement with the draft recommendation	
1. Does the stakeholder agree with the committee's recommendation.	Yes <input checked="" type="checkbox"/>
	No <input type="checkbox"/>
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 <input checked="" type="checkbox"/>
	No <input type="checkbox"/>
No comment.	
Clarity of the draft recommendation	
3. Are the reasons for the recommendation clearly stated?	Yes <input type="checkbox"/>
	No <input checked="" type="checkbox"/>
<p><b>Page 26, Budget Impact, paragraph 2:</b> "CADTH reanalyses ... adopted a higher maintenance dose of cannabidiol ... and assumed 100% adherence to treatment."</p> <p>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<sup>1</sup> and real-world dosing evidence.<sup>2</sup> CADTH's reanalyses represent a higher dose than the recommended maintenance dose in the product monograph and therefore higher annual drug costs than expected in clinical practice for EPIDIOLEX.</p>	
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes <input checked="" type="checkbox"/>
	No <input type="checkbox"/>
No comment.	
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes <input type="checkbox"/>
	No <input checked="" type="checkbox"/>
<p><b>Page 4, reimbursement condition 2:</b> "2. Patients must have the following: 2.1. At least 2 drop seizures per week over a 28-day period prior to initiation of cannabidiol."</p>	

Jazz disagrees with restricting access to EPIDIOLEX to only patients who have at least two drop seizures per week 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 Lennox-Gastaut syndrome (LGS), who experience a variety of developmental and cognitive delays, 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 during a specific time period.

**Page 4, reimbursement condition 5:** "5. Prescribing and monitoring of cannabidiol for LGS should be limited to adult and pediatric neurologists with expertise in the diagnosis and management of patients with LGS."

Jazz disagrees with restricting access to EPIDOLEX to only patients who are under the care of a neurologist. LGS is a complex epilepsy which requires comprehensive management strategies. In practice, while neurologists play a pivotal role in overseeing the treatment of LGS, the nature of this syndrome often necessitates coordinated care involving multiple healthcare professionals. Given the multidisciplinary approach required for effective management of LGS, restricting prescription authority would be challenging as other specialists may be the primary point of care for the patient.

- Many patients with LGS are pediatrics and have their disease managed by pediatricians, as well as neurologists. For other patients who live far away from epilepsy centers, care may be coordinated between their community physician who is experienced in managing epilepsy and their neurologist at the epilepsy center. Therefore, for many patients, pediatricians and family physicians prescribe anti-seizure medications (ASMs) for seizure control.
- Other ASMs that are indicated and funded for LGS and similar developmental and epileptic encephalopathies do not require patients to be under the care of a neurologist. For rufinamide, which is indicated for patients with LGS, CADTH recommended patients be under the care of a physician experienced in treating LGS,<sup>3</sup> 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.<sup>4</sup>
  - 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.<sup>4</sup>

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

<sup>a</sup> CADTH may contact this person if comments require clarification.

<sup>1</sup>GW Research Ltd (2023) (Product Monograph for EPIDIOLEX (cannabidiol)). November 15, 2023.

<sup>2</sup>Jazz Pharmaceuticals (2022) VV-MED-29432 - Epidyolex Daily Dose in LGS and DS - Patient INSIGHTS (INSIGHT Health) Germany. In.

<sup>3</sup>Canadian Agency for Drugs and Technologies in Health (2012). *CDEC Final Recommendation: Rufinamide*. Available online at: <https://www.cadth.ca/rufinamide>. Accessed: April 2024.



<sup>4</sup>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.