CADTH

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

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0799
Brand name (generic)	Cannabidiol
Indication(s)	Dravet Syndrome
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:

- #5: Cannabidiol should not be reimbursed in patients concurrently using cannabis or other cannabinoid-based medications.

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 #5 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.

- #6: A price reduction of 44% would be required for adjunctive cannabidiol to achieve an ICER of $50,000 per QALY compared to usual care alone.

CLAE would strongly recommend retaining the recommendation #6 of implementing "A reduction in price". As you well stated, a price reduction of at least 40-45% 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.		
	Yes	☐

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	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	☐
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	SR0799
Name of the drug and Indication(s)	Cannabidiol (Epidiolex) as adjunctive therapy for the treatment of seizures associated with Dravet Syndrome (DS) 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	☐

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	SR0799-000
Brand name (generic)	EPIDIOLEX (cannabidiol)
Indication(s)	As adjunctive therapy for seizures associated with DS 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 21, Budget Impact, paragraph 2: "CADTH reanalyses … adopted a higher maintenance dose of cannabidiol … and assumed 100% adherence to treatment." 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 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.		
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 4, reimbursement condition 1: "1. Treatment with cannabidiol should be reimbursed in patients with seizures associated DS who meet the following criteria: 1.1. Patients … with at least 4 convulsive seizures per month."		

Jazz disagrees with restricting access to EPIDIOLEX to only patients who have at least four convulsive seizures per month 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 Dravet syndrome (DS), 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 4: "4. Cannabidiol for DS should be prescribed by neurologists or pediatric neurologists with experience in the treatment of patients with DS."

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

- Many patients DS 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 DS and similar developmental and epileptic encephalopathies do not require patients to be under the care of a neurologist. For stiripentol, which is indicated for patients with DS, the Ontario Exceptional Access Program (EAP) criteria requires that the request is submitted by a neurologist *or* pediatrician.[3]
    - Similarly, 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,[4] and the Ontario EAP criteria only requires that the patient is in the care of a physician experienced in managing seizures, not specifically a neurologist.[3]

It is Jazz's position that EPIDIOLEX should be prescribed by a physician with experience in the diagnosis and management of patients with DS, 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-29432 - Epidyolex Daily Dose in LGS and DS - Patient INSIGHTS (INSIGHT Health) Germany. In.
[3]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.
[4]Canadian Agency for Drugs and Technologies in Health (2012). *CDEC Final Recommendation: Rufinamide*. Available online at: https://www.cadth.ca/rufinamide. Accessed: April 2024.