CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

eptinezumab (Vyepti)

(Lundbeck Canada Inc.)

Indication: Migraine

December 1, 2022

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CADTH and do not necessarily represent or reflect the view of CADTH. No endorsement by CADTH is intended or should be inferred.

By filing with CADTH, the submitting organization or individual agrees to the full disclosure of the information. CADTH does not edit the content of the submissions.

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	
Brand name (generic)	Eptinezumab (Vyepti)
Indication(s)	Prevention of migraine in adults who have had at least 4 migraine days per month
Organization	Canadian Headache Society
Contact information[a]	Name: Elizabeth Leroux, MD, FRCPC [redacted]

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.		
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	NA
	No	NA
Unfortunately, the CHS did not provide a Clinician's Input for eptinezumab. We want to underline that this was the consequence of limited capacity from our members and short timelines, not a lack of scientific interest or clinical support for eptinezumab.		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
We make the following points that apply on CGRP antibodies in general, and to eptinezumab in particular. We agree with the CADTH view that CGRP MABs have shown similar results in RCTs and that superiority between them has not been demonstrated. From clinical experience, significant inter-individual variations are seen both for effectiveness and tolerability to migraine treatments. No predictors for response are currently available. a. We are glad to see that 2 trials of oral preventives are required and not 3. This being said, some provinces do not follow these rules, leading to inequity of access to care between provinces. b. Evidence is growing that CGRP antibodies are better tolerated than oral preventives. For many clinicians, if there were no cost issues, CGRP antibodies would be considered as first line treatments.		

Overeem LH, Raffaelli B, Mecklenburg J, Kelderman T, Neeb L, Reuter U. Indirect Comparison of Topiramate and Monoclonal Antibodies Against CGRP or Its Receptor for the Prophylaxis of Episodic Migraine: A Systematic Review with Meta-Analysis. CNS Drugs. 2021;35(8):805-20.
Reuter U, Ehrlich M, Gendolla A, Heinze A, Klatt J, Wen S, et al. Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. Cephalalgia. 2021:3331024211053571.

c. We would like to understand why a response of more than 30% is sufficient for oral preventives when a 50% improvement is required for CGRP antibodies in general. 30% response can be clinically significant for chronic migraine, but even for CM, if better alternatives like CGRP antibodies are available we would not consider a 30% response to an oral preventive to be a sufficient reason to deny a trial of a CGRP antibody. In practice, we see very significant responses to CGRP antibodies even in patients who have tried up to 10 preventives, often with side effects and long periods of lack of effectiveness.

d. The requirement of providing both headache days and migraine days in authorization submissions has pros and cons from the clinician's perspective. It requires more work from both patient and clinician, and in some patients the difference between a headache day and a migraine day is often unclear, especially in CM patients. On the good side, headache days are less disabling than migraine days and the evaluation of intensity is important for the evaluation of response. We recommend that intensity should be taken into account in the evaluation of response, in particular for CM patients.

e. The 30% improvement + HIT6 is clinically sound, but some patients may see mostly an improvement in intensity and still not reach the 30% of frequency. Clinicians usually will defend such cases with precise clinical input regarding other parameters such as response to acute medications, impact on function, impact on mood and sleep etc. Some patients with CM are very severely affected, have tried many treatments and modest improvements are still very relevant to these people. This type of patient usually is not included in RCTs but is often seen in headache clinics.

f. The duration of the initial authorization at 6 months is reasonable. Once a patient has responded to a CGRP MAB though, we recommend subsequent authorizations to be every 12 months at least. Evidence is now available to show that CGRP MABs are not disease modifying and when stopped the migraine attacks recur. Clinicians are already spending a considerable amount of time on forms and asking them to renew every 6 months for a chronic condition is a poor use of medical expertise and time.
Raffaelli B, , et al. Resumption of migraine preventive treatment with CGRP(-receptor) antibodies after a 3-month drug holiday: a real-world experience. *J Headache Pain*. 2022;23(1):40.

g. It is extremely important that CGRP antibodies can be prescribed by general practitioners. They should not be limited to specialists. Migraine is very prevalent, and the majority is treated in primary care. Waiting lists for headache specialists and even neurologists are very long. Imposing a neurology consultation to access CGRP antibodies would significantly restrict access to care with no medical justification.

h. The combination of Botox and CGRP antibodies is now frequently used by headache specialists. The CHS has issued a documented letter with references which we will provide. Pharmaceutical companies are not going to fund a combination trial. This should not preclude this useful and safe combination for severely affected patients.
i. Evidence suggests that patients who do not respond to or do not tolerate a CGRP antibody have around 30% chance or responding another. It is very important to allow different CGRP antibodies to be tried for a given patient.
Overeem LH, et al. Effect of antibody switch in non-responders to a CGRP receptor antibody treatment in migraine: A multi-center retrospective cohort study. *Cephalalgia*. 2022;42(4-5):291-301.

j. [redacted]
Therefore, the pharmacoeconomic analyses should be updated accordingly.

[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		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
3. 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: • Elizabeth Leroux • Tasjeel Ansari, MD, FRCPC, DABPN • Lik Hang Tommy Chan, MBBS, FRCPC, DABPN • Elizabeth Leroux, MD, FRCPC • William Kingston, MD, FRCPC, FAHS		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Danny Adel Monsour*
Position	*Headache neurologist*
Date	*29-11-2022*
☒	**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**
Lundbeck (Honoraria)	☒	☐	☐	☐
Abbvie (Honoraria)	☒	☐	☐	☐
Eli Lilly (Honoraria)	☒	☐	☐	☐
Miravo (Honoraria)	☒	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	Tasjeel Ansari, MD, FRCPC, DABPN
Position	Headache Neurologist
Date	09/10/2022
☒	**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**
AbbVie (Honoraria)	☒	☐	☐	☐
Lundbeck (Honoraria)	☒	☐	☐	☐
Eli Lilly (Honoraria)	☒	☐	☐	☐
Miravo (Honoraria)	☒			

New or Updated Declaration for Clinician 3	
Name	Elizabeth Leroux, MD, FRCPC
Position	Headache Neurologist, Past President - Canadian Headache Society
Date	*30-11-2022*
☒	**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
Abbvie/Allergan			X	
Eli Lilly			X	
Lin Pharma	X			
Lundbeck			X	
McKesson		X		
Miravo		X		
Novartis			X	
Paladin Pharma	X			
Teva			X	

New or Updated Declaration for Clinician 4	
Name	William Kingston, MD, FRCPC, FAHS
Position	Headache Neurologist, Board member – Canadian Headache Society
Date	*30-11-2022*
☒	**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
Teva			x	
Novartis			x	
AbbVie/Allergan			x	
Eli Lilly			x	
Miravo		x		
Lundbeck		x		

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0743
Name of the drug and Indication(s)	Eptinezumab (Vyepti) for the prevention of migraine in adults
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 Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information			
CADTH project number	SR0743-000		
Brand name (generic)	Vyepti (eptinezub)		
Indication(s)	Migraine		
Organization	Canadian Migraine Society		
Contact information[a]	Name: Maya Carvalho [redacted]		
Stakeholder agreement with the draft recommendation			
1. Does the stakeholder agree with the committee's recommendation.		Yes	☐
		No	X

- **Reimbursement Criteria #2 - Implementation Criteria:**

"Inadequate response to oral prophylactic therapies is defined as less than a 30% reduction in frequency of headache days to an adequate dose and duration of at least two prophylactic medications, which must be of a different class."

Comment: There are many reasons why a person living with migraine may have failed a preventive that are outside the scope of a <30% reduction. Many people cannot tolerate the copious side effects involved with most oral daily preventives. Side effects can include extreme brain fog, numbness and tingling, or dizziness and fainting. We strongly urge you to allow a patient's physician to determine what is deemed a "failure".

- **Reimbursement Criteria #5: Reibursement Condition**

"The physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as a reduction of at least 50% in the average number of migraine days per month…"

Comment: it is widely accepted that success with a migraine preventive medication is determined by assessing BOTH the frequency and the intensity of each migraine attack. For many people taking anti-CGRP medications, their frequency (MMDS) may remain consistent but the intensity of their attacks may be greatly diminished. A reduction in intensity can make a huge difference in the quality of life of the patient, and in their ability to work, take care of their families etc. We cannot exclude this cohort of patients who could benefit so greatly from Vyepti.

- **Reimbursement Criteria #5 - Implementation Criteria**

"Some jurisdictions may want to include a reduction of at least 30% in the number of headache days per month and an improvement of at least five points in the HIT-6 score, compared with baseline, as an alternative criterion for renewal of reimbursement."

Comment: While some jurisdictions CAN implement this more nuanced approach to determining success of a migraine preventive, in practice, only one province, Ontario, agreed to this criteria with other anti-CGRPs. We feel that Criteria #5 should simply state that a reduction of 30-50% reduction in frequency OR a 5 point reduction in the HIT-6 score will be accepted. This recognizes that vast array of patient responses in this very complicated disease.

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	X
	No	☐
If not, what aspects are missing from the draft recommendation?		
Clarity of the draft recommendation		
3. **Are the reasons for the recommendation clearly stated?**	Yes	X
	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	X
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	X
	No	☐
If not, please provide details regarding the information that requires clarification.		

[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	*Maya Carvalho*
Position	*Founder, Canadian Migraine Society*
Date	*29/11/2022*
X	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	X
	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	X
	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	X

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**
Lundbeck	X	☐	☐	☐
Abbvie	X	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0743-000
Brand name (generic)	Eptinezumab (Vyepti)
Indication(s)	Prevention of migraine in adults who have had at least 4 migraine days per month
Organization	Migraine Canada Migraine Quebec
Contact information[a]	Wendy Gerhart (Migraine Canada) Leona Heillig (Migraine Quebec)

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.

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?

In our submission we rationale on how accessing new treatment options was important to the community. The current options available are not optimal. They have intolerable side effects and are simply not effective for many. Patients and healthcare professionals should have access to new, innovative medications approved by Health Canada to be safe and effective. It is essential patient's and clinicians have multiple options to help manage migraine.

We believe patient input submissions should have more weight and consideration. The content that feeds into our submissions is what Canadians experience daily and how they are impacted. Migraine negatively impacts almost all aspects of people's live including ability to work, cognitive functioning and more.

Clarity of the draft recommendation

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

We firmly believe that with the current medications available, patient needs continue to NOT be met and there is a need for more options and access to new treatments to help Canadians better manage their condition.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

It is clear that the recommendation from the committee is to reimburse Vyepti with some conditions. We are extremely appreciative.

In response to the reimbursement conditions and reasons we have the following comments:

1. No Comments

2. It is positive that 2 trials of oral preventives are required vs patients needing to try and fail on 3. We will be advocating to all provinces to follow these recommendations to ensure Canadians have equitable access to medications regardless of the jurisdiction they reside. Consideration should also be given to medication being intolerable due to side effects as a reason to discontinue therapy. Lastly, for a significant number of severe patients, the combination of a CGRP + Botox is effective and should be considered. There are no safety issues with this combination. Patients also share that the newer medications, like CGRP antibodies, are better tolerated and more effective than the oral preventives.

   We question why a response of more than 30% is sufficient for oral preventives when a 50% improvement is required for CGRP antibodies in general. If a patient has a 30% response, this can be significant to the patient and his/her quality of life. Patients strive for reduction in frequency and/or intensity.

3. Asking patients to track both headache days and migraine days is challenging. For some people, the difference between a headache day and a migraine day isn't clear and could be captured incorrectly. Intensity is important for the assessment in response. For some, a less intense migraine attack makes a significant impact on quality of life. We feel strongly the recommendations be changed to incorporate intensity as a consideration.

4. Initial authorization for 6 months is reasonable with subsequent authorizations to be every 12 or 18 months. Asking physicians to do excessive paperwork every 6 months is inefficient use of their time. Migraine is chronic. There is no cure. When patients respond and do well to a CGRP, its essential they continue to take it without breaks. We have heard from patients that when they have taken and are well managed with a CGRP and then come off, their migraine attacks come back.

5. We disagree with this recommendation. The 30% improvement + HIT6 is reasonable clinically but some patients may see mostly an improvement in intensity and still not reach the 30% of frequency. Reduction in intensity can greatly impact quality of life and improve ability to work, function, improve mood, sleep, mental health, etc. For some patients severely affected and who have tried multiple treatments, modest improvements are very relevant. There is also evidence suggesting that patients who do not respond to, or do not tolerate, a CGRP antibody have around 30% chance of responding another. It is important to allow patients to try different CGRPs.

6. See point 4.

7. While we agree an accurate diagnosis of migraine is important, due to the shortage of headache specialists and access to neurologists in general, prescriptions by primary care providers is essential. Due to the prevalence of the migraine, the majority of patients are treated by a primary care clinician. There are simply not enough headache specialists / neurologists in Canada to treat everyone who has a migraine diagnosis. Making this mandatory is not efficient or responsible use of healthcare resources (human and financial).

8. While we agree there shouldn't be a premium for eptinequmab over other CGRP's, consideration should be given to dosing frequency and method (ie. injection vs infusion). There is obvious costs involved with infusion medications that other manufacturers don't have. We also don't feel difference in price be a barrier in people receiving eptinequmab as an option.

[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	*Wendy Gerhart*
Position	*Executive Director*
Date	*30-11-2022*
☒	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. Dr. Elizabeth Leroux (Chair, Migraine Canada and practicing neurologist in Montreal)		
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

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0743-000
Brand name (generic)	VYEPTI® (eptinezumab)
Indication(s)	For the prevention of migraine in adults who have at least 4 migraine days per month.
Organization	Lundbeck Canada Inc.
Contact information[a]	[redacted]

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

Lundbeck Canada Inc. (Lundbeck) agrees with the committee's recommendation that eptinezumab be reimbursed for the prevention of migraine in adults who have had at least 4 migraine days per month in line with the conditions listed in Table 1 of the document. The recommendation and conditions are consistent with the evidence reviewed by the CADTH team, and are also consistent with the previous recommendations for other anti-CGRPs.

Lundbeck is suggesting a few general editorial changes, as follows:

- For clarity and consistency regarding the condition that the total cost does not exceed the cost of treatment with the least costly reimbursed anti-CGRP, Lundbeck requests that the following underlined text in the 7th Discussion Point on pg. 6 be removed: *"The use of IV infusion may be associated with increases in health care resource utilization (e.g., infusion time, nursing time, etc.).* [redacted] It is important to consider that there are other aspects beyond the pricing of eptinezumab (e.g., cost of infusion) that can be explored during implementation to ensure that the total system cost of eptinezumab does not exceed the cost of treatment with the least costly reimbursed anti-CGRP. [redacted]

- Lundbeck is requesting a change in the 5th paragraph on pg. 16, where it was noted regarding the NMA that *"…arm-based models do not preserve randomization, hence comparative estimates are at a greater risk of bias in relative treatment effects."* The criticism that arm-based models do not preserve randomization and that comparative estimates are therefore at a greater risk of bias in relative treatment effects is not accurate. The NMA was conducted using contrast-based parameterization, where the information on the relative treatment effects is coming only from within trials, and not across trials. Therefore, despite using an arm-based model, the independent baseline model preserves randomization within trials. Thus, the criticism of greater risk of bias in relative treatment effects is unfounded. Lundbeck kindly requests that the 2nd sentence of the paragraph be revised as follows: *"Given the absolute outcome measures considered in the analyses, this was considered appropriate, as contrast-based parameterization used in the NMA approach preserves randomization, hence comparative estimates are not at a greater risk of bias*

in relative treatment effects."

- At the end of the 6th paragraph on pg. 16, Lundbeck is requesting the addition of the following text to provide context regarding the limitations of using a random effects model, and why a fixed effects model was used for the NMA (this text is taken directly from the clinical review report): *"The sponsor noted that due to the lack of studies per treatment comparison, the between-study heterogeneity could not be informed by the data, and random-effects models generated implausible results and were only conducted as secondary for the main outcomes of change from baseline in MMD and 50% MRR."*

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	☐

N/A

Clarity of the draft recommendation

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

N/A

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒

Lundbeck is not requesting any changes to the proposed Reimbursements Conditions and Reasons, as presented in Table 1 of the recommendation. However, Lundbeck would like to provide feedback regarding two items within the Implementation Guidance.

First, as it relates to the definition of inadequate response to oral prophylactic therapies within the Implementation Guidance on pg. 4 (i.e., *"30% reduction in frequency of headache days to an adequate dose and duration of at least two prophylactic medications, which must be of a different class"*), Lundbeck recognizes that these criteria have been implemented by select participating drug plans for other anti-CGRPs; however, not all participating drug plans have specified the exact definition of inadequate response to oral prophylactic therapies. Current guidelines and clinical expert opinion suggest that a 50% reduction in frequency of headache days may also be an appropriate threshold for determining response to oral prophylactic therapies.[1-4] For example, expert consensus within the 2012 Canadian Headache Society guideline for migraine prophylaxis, which focused on oral prophylactic therapies, is that a prophylactic medication is usually considered effective if migraine attack frequency or the number of days with headache per month is reduced by 50% or more, although lesser reductions in migraine frequency may be worthwhile, particularly if the drug is well tolerated.[1] This is consistent with the clinical input summarized in the CDEC recommendation; although in the context anti-CGRPs, it is noted that a clinically meaningful response could include a reduction in monthly headache days (MHD) and monthly migraine days (MMD) and a 50% responder (50% reduction in MMD).

Second, within the Implementation Guidance on pg. 4, CDEC suggests that *"There is no evidence to support the combination of eptinezumab with onabotulinumtoxinA; therefore, these drugs should not be used together."* However, in response to the implementation issue raised on the same topic on pg. 10, the clinical expert consulted by CADTH noted *"…there is data for onabotulinum toxin A combined with other monoclonal antibodies. Based on this, the clinical expert suggested that eptinezumab could be used with onabotulinum toxin A. CDEC was in agreement with the response from the clinical*

expert consulted by CADTH." Lundbeck also agrees with the commentary made by the clinical expert on pg. 10 and believes the text on pg. 10 contradicts the Implementation Guidance on pg. 4 to not use eptinezumab and onabotulinumtoxinA.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
N/A		

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

REFERENCES

1) Pringsheim T, Davenport W, Mackie G, Worthington I, Aubé M, Christie SN, Gladstone J, Becker WJ; Canadian Headache Society Prophylactic Guidelines Development Group. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci. 2012 Mar;39(2 Suppl 2):S1-59.
2) Silberstein SD. Preventive Migraine Treatment. Continuum (Minneap Minn). 2015 Aug;21(4 Headache):973-89.
3) Ha H, Gonzalez A. Migraine Headache Prophylaxis. Am Fam Physician. 2019 Jan 1;99(1):17-24.
4) Ailani J, Burch RC, Robbins MS; Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021 Jul;61(7):1021-1039.