CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

LEMBOREXANT (Dayvigo)

(Eisai Limited)

Indication: For the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

September 2, 2022

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	
Brand name (generic)	**Lemborexant (Dayvigo)**
Indication(s)	**Insomnia**
Organization	**National Advisory Board (Dr. Pierre Chue)**
Contact information[a]	**Pierre Chue** [redacted]

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

I speak on behalf of a group of Canadian physicians with expertise and experience in treating insomnia and other sleep disorders who are deeply concerned about the decision of CADTH to not recommend the reimbursement of lemborexant. It is clear that more options are needed in the current treatment of insomnia that are effective and safe compared to existing treatments or no treatment. In our opinion, based on the trial data and clinical experience lemborexant meets this unfulfilled and urgent need.

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	☒

The group emphasized the lack of safe options for the modern management of insomnia despite the prevalence as well as the consequences of inadequate treatment of insomnia.

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

The reasons are contradictory and not clinically relevant. Efficacy should be the primary outcome measure - this is the goal of registration trials and the reason for approval of lemborexant by HC, FDA and EMA. PROs are important but secondary measures and are confirmed in any event by reports from the physicians, patient testimony and patient groups. The study populations are reflective of the data required for registration for short-term and longer term use and consistent with clinical practice. While comorbidities are frequent, as also identified by the physician group, if these were the study populations primary efficacy would be difficult to demonstrate. The reality is clinical practice is always extrapolated to these groups as exists form the current approved medications for which no such data exists other than the well documented risks.

The existing approved classes of medications (benzodiazepines and Z-drugs) are associated with dependence and habituation and this is a concern expressed by patients. Orexin-antagonists have not been similarly associated given their MOA which is not a GABA – A mechanism.

Finally, in the absence of Canadian guidelines the conclusions should be based on registration approval criteria and clinical input from front line treating physicians. The CADTH clinical expert agrees with the risks posed of existing medications and the consideration of lemborexant as a first-line treatment.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
The implementation issues are clearly identified but as discussed in the response to question #3 they are not considered objectively with a clinically relevant lens that puts the real difficulties that patients face foremost.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
The alternative medications suggested are not consistent with clinical practice. Mirtazapine is associated with significant weight gain (greater risk in females) and unacceptable/inappropriate for many patients already struggling with obesity. Doxepin is a tricyclic antidepressant with anticholinergic side effects and at a rebranded 6 mg dose for insomnia is many times more expensive than generic doxepin at higher antidepressant doses. Zopiclone is a special access drug within NIHB thus benzodiazepines are prescribed which contribute directly to addiction problems in vulnerable populations. It is clinical reality that most patients do not follow the directives concerning not driving after taking zopiclone (risks are even greater with zolpidem). The need for safer medications is clear and the trial data is supportive of lemborexant in this regard.		

[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	*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 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	☐
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐

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	☐	☐	☐	☐

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	☐
If yes, please detail the help and who provided it.		
3. 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		
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	*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 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	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
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 5	
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	☐	☐	☐	☐

Stakeholder information	
CADTH project number	SR0716-000
Brand name (generic)	Lemborexant
Indication(s)	Insomnia
Organization	Canadian Consortium of Sleep and Sleep interested Physicians (CCSSP)
Contact information	Dr. Atul Khullar [redacted]

1. Does the stakeholder agree with the committee's recommendation. – 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.

Page 3: "Magnitude of treatment was inconsistent and of uncertain clinical importance"
"Uncertain if result was clinically meaningful because of lack of MID or clinically important thresholds for clinical effect.*"*MID and clinically important thresholds have not been well established in this area because many agents used in Canada are off label and have very little or no randomized control data. CDEC also did not postulate what clinically significant or MID levels would be. We noted a change in the insomnia severity index (ISI) score of 7 or greater is a clinically meaningful improvement of insomnia symptom severity, whereas an absolute value on the total ISI score of below 8 indicates a remission from insomnia (1.) These were both met for the most part by lemborexant in Sunrise 1 and 2 (2, 3). **This expert group of researchers and clinicians feels compared to all other insomnia trials the lemborexant effect size is consistent, comparable to other agents and clinically significant.**

All subjective outcomes in 6 months and few reached suggested thresholds for clinically important effect" – Long term subjective outcomes are standard in insomnia trials. The clinical expert consulted by CADTH indicated that subjective outcomes are likely more important in treatment, yet CDEC contradicts this by criticizing this.

"**It was uncertain if the differences in treatment effects observed would be experienced by patients with comorbid conditions such as sleep apnea, anxiety, and depression because those patients were excluded from the trials based on the exclusion criteria."** This is another contradictory and factually incorrect statement. Although severe patients were excluded, almost 15% of patients in Sunrise 1 and 2 had mild depression and anxiety, 44% were on antidepressants, and the effect sizes of lemborexant were similar in the depression/anxiety subgroup. 40% of patients had mild sleep apnea (AHI 5-15) in the studies. CDEC also later acknowledges on P. 10 – **"In general, the clinical expert consulted for this review confirmed that the populations were similar to patients seen in Canadian clinics and the trial results would be generalizable with some limitations.** CDEC dismisses the comment of their own expert that study population was generalizable without any good rationale. 50% of the patients in Sunrise 1/2 had a major comorbidity – this is an improvement on previous insomnia trials and some of the most generalizable RCT evidence in the field. Our feedback also noted that clinically we find the trial data to be generalizable in clinical practice as well.

"The indirect evidence comparing lemborexant to other drugs is uncertain" - ***There*** often isn't direct evidence comparing to drugs used in Canada in most therapeutic areas and the NMA limitations noted on page 4 are not out of keeping with standard indirect evidence studies. It is unreasonable to ask for data that is different from other hypnotics, especially given the dearth of approved and safe options in Canada.

"No direct evidence comparing efficacy and safety to commonly used drugs used in Canada." Zolpidem-ER and zopiclone are very comparable clinically as they are of the same drug class and have a shared mechanism (4), hence a lack of direct comparison is not a critical issue. The risks of the z-drugs and benzodiazepines have been clearly documented in many guidelines and metanalyses and the lack of next day side effects of lemborexant has been studied thoroughly (5). Although statistically limited, the lack of a signal is clinically important in comparison with clearly documented harms with other indicated agents.

"CDEC couldn't conclude whether safety profile of lemborexant was safer." Though absolute certainty and direct comparison is not available here, the clear signals for lack of abuse potential, limited risks of fall, driving and postural stability is reassuring compared to the documented risks of fall and driving harms for other indicated agents, unknown issues with off label treatments, as well as the high incidence of self-medication of insomnia with OTC agents, cannabis and alcohol. Also, the analysis of risk of falls in the report simply not put into context. Even though the reduction of fall risk can't be conclusively noted, the signal for postural stability (5) plus the lack of a fall

signal is critical, as nearly every other drug used on or off label for insomnia has demonstrated a fall risk (6,7). **If CDEC cannot conclude that safety profile is better, they should review the extensive clinical feedback provided.**

"The lack of withdrawal or rebound insomnia after long term treatment was minimized by stating that patients were only followed for 2 weeks after discontinuation." We feel that 2 weeks is long enough to establish a signal for lack of physical rebound/dependence. CDEC did not note the negative results in all 3 non-clinical abuse studies, the lack of evidence of binding at receptors associated with abuse potential nor diversion and dependence of study medication during clinical development, and the low incidence of TEAEs associated with abuse potential.

"Although patients expect new treatments for insomnia to have long-term effectiveness, fewer side effects, and result in uninterrupted and restorative sleep, less stress and anxiety, improved productivity, and improved relationships, no definitive conclusion could be reached regarding whether these needs were met by Lemborexant" - Yet again, the report later contradicts this and acknowledges on p 10 that "**Most outcomes identified in the input received by CADTH from patient groups aligned with efficacy and harms outcomes in the studies though there are still gaps in the evidence for the use of LEM in patients with comorbid conditions and alongside other medications."** CDEC also acknowledges that safety efficacy profile does align with patient stakeholder needs. Both long term efficacy and more uninterrupted sleep were demonstrated from the data dismissed. Additionally, on p7, patient reported outcomes (which would reflect clinical importance to the patient) were dismissed based on being secondary or exploratory outcomes. This tone is inconsistent. CDEC also doesn't explain why term effectiveness and safety can't be imbued from 12-month data. This is the longest-term data for any hypnotic in the Canadian market and by comparison it is similar to most approved and publicly funded antidepressants.

"Patients expressed concern about managing sleep problems without dependence and serious side effects." Although the goal is always to manage insomnia disorder as best possible with CBT-I and without medication, pharmacological therapy is a reality in the insomnia landscape. 30-40% in clinical trials demonstrate nonresponse or dropout from CBT-I (9,10), the effect size is diminished with anxiety, (11), CBT-I compliance is poor with comorbidities (12) and there remains a severe lack of CBT resources in Canada, and patients often do not want or choose CBT-I. A common clinical practice is also the combination of pharmacotherapy with CBT-I and more agents are needed.

Insomnia is clearly a chronic illness with up to 46% continuing to have symptoms over a 3-year period. (13) However, almost all the indicated agents have black box warnings outside of short-term use and difficult clinical decisions often face Canadian clinicians treating insomnia. And though it is unclear if lemborexant is more effective than other indicated drugs for insomnia in Canada, there are no concerning safety signals outside of somnolence, so as clearly and repeatedly noted in the clinical feedback, lemborexant has allowed clinicians across the country to use less off label agents, benzodiazepines/z-drugs and increased the comfort and acknowledgement of safely treating insomnia. **This agent's unique mechanism and more benign safety profile has allowed it to rapidly become standard of care for many insomnia patients who require pharmacotherapy. We clearly noted that some of these needs that CDEC was uncertain about have been met in our clinical experience by lemborexant and this was not reflected in the report.**

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH? – NO
If not, what aspects are missing from the draft recommendation?

To be blunt, there is very little evidence that the committee even considered our major conclusions and thorough feedback reflecting a nationwide consortium. It was given one line in the report and there is no evidence of any of our conclusions were integrated. We did note that there has been a marked shift in the treatment paradigm, there were clear reasons to try lemborexant before other treatments, there were certain patients (such as the elderly and substance abuse patients) would be suited for this drug and that the mechanism was quite distinct. Evidence was cited for these claims. As noted above, any of the things CDEC was "uncertain" of in their discussion points have been clearly noted clinically in many patients with evidence and was stated in our feedback.

3. Are the reasons for the recommendation clearly stated? - NO
If not, please provide details regarding the information that requires clarification.

The protocol and process for selected studies is also not clear in the report. Clarity on studies that were discounted and why was not given. A lack of adjustment for multiple comparisons does not completely invalidate the signals for lemborexant in the patient reported and secondary outcomes. While perhaps useful in other therapeutic areas, these sorts of analysis penalize areas that have less established targets. Also, in contradiction to the report, the FSS was significantly improved at 6 months (14).

Clarity is also needed is to why lemborexant is being held to a much higher standard than other approved treatments in insomnia with clear risks and limitations. The tone of this report has unrealistic expectations of what the data can provide in this therapeutic area and asks for a level of certainty that could only be answered with studies that are fundamentally impractical. There is a balance between internal and external validity in clinical trial medicine and this is especially challenging in insomnia research. **Providing guidance on what CDEC believes are appropriate trial goals and data, which must be achievable and realistic for the study population, would be more helpful and fulfill the articulated need for more accessible treatments.**

4. Have implementation issues been articulated and adequately addressed in the recommendation? – NO
If not, please provide details regarding the information that requires clarification.

Page 13: Economic evidence: Though doxepin and mirtazapine could be comparators, only doxepin is indicated. It is also not noted that two of the comparators are off label (quetiapine and trazadone), neither are usually recommended and one (quetiapine) has well known significant harms.
Page 14: As noted above, the report indicates marked uncertainty about efficacy and whether lemborexant can meet the needs of patients, yet CDEC uses the feedback from their expert to "assume a higher market share of lemborexant". Again, this is contradictory.
Question 5. NOT APPLICABLE

CCSSP Feedback Conclusion
Although there are limitations in the data set, the actual comments and contradicting statements in the current CDEC response show a fundamental misunderstanding of the nature and clinical realities of insomnia disorder in Canada. The response also demonstrates unreasonable expectations and a lack of contextual understanding of limitations of standard research studies that constitute the body of evidence for pharmacologic intervention for insomnia disorder. The word uncertain is used frequently in the report. This to our group appears to be less about the actual data and more a lack of understanding of the therapeutic area.

Unfortunately, this was further compounded by not reflecting the conclusions from a group of seasoned clinicians and researchers with national and international experience who provided thoughtful evidence-based feedback. There is a concerning trend of simply not integrating or even acknowledging clinicians across Canada who actually treat these disorders in recent CADTH reports. This to us appears to be a systemic issue and may reduce innovation and access. **This was seen a number of years ago with the common drug review (CDR) assessments of cancer treatments leading to specialists, payers and patient groups testifying in front of a House of Commons committee leading to the subsequent creation of a separate panel to assess these drugs (15). We would advocate for something similar in agents that affect the central nervous system.**

All the clinicians in our group strongly feel lemborexant is a critical first line tool for the pharmacological treatment of insomnia a disorder which is under-recognized, inappropriately treated and associated with tremendous morbidity and mortality. The agent is part of our practice and though not for many patients, all of us have had dramatic responses with, often getting them off other more toxic and off label prescription medications for insomnia, over the counter medications, alcohol and cannabis. The currently indicated agents with public coverage (zopiclone and the benzodiazepines) are only used as a last resort, as their harms are well documented, guidelines discourage prescribing, and many people in clinical practice fail both agents quickly. More indicated options that are accessible are desperately needed to help change and perhaps save the lives of countless patients who shouldn't be exposed to these agents (16).

Given its strong linkages and high level of comorbidity with mental health concerns such as depression and anxiety, insomnia could very well be considered a mental health disorder. The Government of Canada has repeatedly acknowledged the existence of a mental health crisis, and this has worsened due to the COVID pandemic, and have made a commitment to improve treatment and funding. Insomnia has also worsened with the pandemic and potentially limiting access to an indicated and treatment with advantages in tolerability such as lemborexant is discordant with the government's objectives.

We can understand that the resources of our public system are finite and given the rampant prevalence of insomnia, that potential utilization of this treatment may be a concern, but not all patients respond to pharmacological treatment nor lemborexant. **We strongly feel that some path to public coverage is necessary given the lack of options to treat insomnia disorder and the reasonable lemborexant data. This response from CDEC to not reimburse this agent further stigmatizes and marginalizes the most vulnerable of the 13% of Canadian patients with insomnia disorder require the public formulary. It will continue the entrenched pattern of Canadians commonly using more toxic or off label substitutes to treat their insomnia disorder with much greater societal risks of harm.**

CADTH

Appendix 2. Conflict of Interest Declarations for Clinician Groups

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
2. 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		
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	☐
Unchanged: **Dr. Atul Khullar, Dr. Charles Morin, Dr. Charles Samuels, Dr. Jeffrey Habert, Dr. Jennifer Swainson, Dr. Raymond Gottschalk, Dr. Thanh Dang Vu, Dr. Alex Desautels, Dr. Michael Mak, Dr. Alan Lowe, Dr. Martin Katzman, Dr. Serge Lessard, Dr. Roger McIntyre, Dr. Pierre Blier, Dr. Roumen Milev**		

References for CCSTP feedback document

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CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0716
Name of the drug and Indication(s)	Lemborexant (Dayvigo) for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.
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	SR0716
Brand name (generic)	Lemborexant (Dayvigo)
Indication(s)	Insomnia
Organization	Menopause Chicks
Contact information[a]	Name: Shirley Weir

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.

I am worried about women. My disagreement is more disappointment. 77% of women in my community (predominantly 45-55) are experiencing poor sleep one or more times per week and it's negatively impacting cognitive function, mood, energy and ability to exercise, responsibilities in the family, at work and in the community. 827 women (out of 1XXX) told me that IF sleep aids were offered (Z-drugs, Benzodiazepines, Gabapentin and more) by their physician, they had stopped taking due to adverse side effects.

But the patient stories shared by women who had tried Lemborexant were encouraging. One women shared that she had not slept through the night for 12 years and now she was able to resume gainful employment because her sleep was back on track. Three prescribers (MD, Ob/Gyn, NP) shared patient success stories of individuals who had all tried a long list of sleep solutions and who, under the care of their physician, were finally rating their ability to function at higher than 70% for the first time in years.

I understand this project is about a recommendation for reimbursement. Considering the degree to which women pay an additional "tax" (expenses) for healthcare (menstruation, contraception, menopause), it is my hope this solution is adequately reviewed and reconsidered so that women who need relief from insomnia have fair access.

Thank you.

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?

Possibly the patient stories (videos in original feedback) underscoring how often reimbursed medications are prescribed in an "off label" format for the treatment of insomnia. Gabapentin was mentioned over and over again in our member research/patient dialogues

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.		
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.		

[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	*Shirley Weir*
Position	*Founder, Menopause Chicks*
Date	*09-06-2022*
☒	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.		
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**
Eisai	☐	☐	☒	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0716-000
Brand name (generic)	Lemborexant
Indication(s)	Insomnia
Organization	Migraine Canada
Contact information[a]	Wendy Gerhart

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.

The draft recommendations state that "Although patients expect new treatments for insomnia to have long-term effectiveness, few side effects, and result in uninterrupted and restorative sleep, less stress and anxiety, improved productivity, and improved relationships, no definitive conclusion could be reached regarding whether these needs were met by Lemborexant. Patients also expressed concern about being able to manage their sleep problems with becoming dependant on pharmacological treatments for insomnia and it was unclear if Lemborexant would address this need".

Our submission was based on community feedback that validated insomnia as a serious complication for many people who live with migraine and that current options are not effective and can be dangerous (addictive). Our survey results validate sleep, or lack of sleep, has a significant impact on their condition and are desperate to solve their insomnia as one component to managing their migraine attacks. Many, many patients commented that although sleep is a major issue, the side effects and chance of dependency was a huge consideration in choosing to NOT take these old, intolerable and addictive medications.

The majority of our survey respondents are clearly dissatisfied with current options and welcome new options and that they want to be able to manage sleep problems without becoming dependant. Studies on Lemborexant demonstrate strong evidence of being effective with less and more tolerable side effects with less change of dependency. Choice of treatment options and access is critical.

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 included how accessing new treatment options was important to patients. The current options are not optimal and include horrible side effects and dependencies. Patients and healthcare professionals should have access to new, innovative medications approved by Health Canada to be safe and effective.

We believe patient input submissions should have more weight and consideration. The content that feeds into submission is what Canadians are experiencing on a day-to-day basis and how they are being impacted. Insomnia is one of the top complications experienced by patients with migraine. It negatively impacts many aspects of people's live including ability to work, cognitive functioning and more. No aspect of life is not impacted by insomnia.

It cannot be emphasized enough the patients should have access to options; particularly first in class, innovative options.

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.

We firmly believe that with the current medications patient needs are NOT being met and there is a significant unmet need for options and access to new treatments to help manage insomnia. There is value with proven benefit of Lemborexant that current options don't offer Canadians.

We pointed out in our submission there is a significant link between sleep, headache and mood. The same brain regions and chemical messengers impact sleep, headache and mood, so inadequate or poor quality sleep increases the odds for headache and mood change. For example, people living with migraine who also experience insomnia often suffer from anxiety and/or depression, which are also common migraine comorbidities.

At the University of North Carolina (UNC), Chapel Hill, researchers studied the association between sleep and migraine. The researchers attempted to see if making changes in sleep patterns could have an effect on migraine frequency and intensity. 43 women with chronic migraine were randomly placed into one of two groups. The first group received formal instructions on how to improve their sleep habits. The other received placebo instructions. They were asked to keep a diary of their headaches. Six weeks later at follow-up, women who changed their sleep behavior **saw a significant improvement in headache frequency and intensity**. **Dramatic improvement was seen in one of three, to the extent that they no longer met criteria for chronic migraine**. The point of including this information is to validate that managing insomnia whether through good sleep habits or medication has an impact on migraine frequency and intensity.

Another study completed in 2018, showed through controlled trials a decrease migraine frequency for insomnia trigger and that **sleep management should be complimentary to standard headache practice.**

When looking at budget implications, it is important to consider and the cost of not treating. There was a study recently done by Casper and Gallup to study sleep. Over 3,000 adults (10 years+) living in the states participated. The American economy loses an estimated $44.6 billion annually in unplanned absenteeism as a result of poor sleep among workers. There are other studies that indicate there is a direct cost to our GPD due to presenteeism caused by poor sleep. So when we are only looking costs associated with covering these medications, considerations with the connections with societal costs of not covering these medications. Additionally, better sleep impacts many complications experienced diseases.

According to a study done in Canada on 28,000 employees on 16 health conditions, migraine came **third** for cost related to missed days at work after back pain and mood disorders. Migraine was more costly than asthma, diabetes, cancer and arthritis. (Zhang)

- Among Canadian employees, **56%** had taken sick days, **23%** were on short term disability, and **18%** were on long term disability.
- Migraine Canada found that only **20%** of people with migraine (all severity) did not miss days of work. **36%** missed between 4 and 16 days per year.
- **25%** reported being disabled.

Given that insomnia is one the most common co-morbidities migraine patients experience, effectively managing sleep can make a profound difference to a migraine patient (4.3 million Canadians live with migraine).

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.

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.

It is clear that the recommendation from the committee is to not reimburse Lemborexant.

We hope the reviewing committee with reconsider. Patients are desperate for new options that have fewer side effects and less chance of dependency to help manage co-morbidities that have a direct impact on their primary diagnosis (in this case Migraine). The CADTH recommendation to not reimburse will deny patients access to a first in class medication that has demonstrated to be effective.

[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	*07-09-2022*
☒	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.		
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	SR0716-000
Brand name (generic)	Lemborexant
Indication(s)	Insomnia
Organization	Mood Disorders Society of Canada
Contact information	Name: Dave Gallson

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.

In the Draft Recommendations, it states within the Rationale for Recommendations section that "*Although patients expect new treatments for insomnia to have long-term effectiveness, fewer side effects, and result in uninterrupted and restorative sleep, less stress and anxiety, improved productivity, and improved relationships, no definitive conclusion could be reached regarding whether these needs were met by lemborexant. Moreover, patients expressed concern about being able to manage their sleep problems without becoming dependent on pharmacological treatments for insomnia, and it was unclear if lemborexant would address this need*."

Yet throughout our MDSC Patient Group submission, which was based on a very wide and in-depth national Sleep and Mental Health survey to understand sleep behaviours and how sleep problems such as insomnia impact our mental health, and how mental health issues can also impact our sleep.

MDSC hired the independent research firm Narrative Research to conduct the survey and analyze the results,

Our research objectives included:

- Delineating the different profiles of sleep disturbances in people with/without symptoms of mental disorders.
- Understanding the perceived impacts of sleep problems on mental health and daily functioning.
- Characterizing levels of knowledge about sleep and what topics are of greatest interest.
- Identifying the use and perceived effectiveness of various types of sleep treatments and therapies.

The online survey of the general population was conducted with a random sample of **1,200 respondents** across Canada. In addition, MDSC shared a survey link through its network (notably on social media), resulting in **49 additional surveys** being completed. Quotas were applied to the general population survey based on age, gender and region, while the survey results were also weighted on those characteristics. In addition to the questions included on the general population survey, the network survey included a few more questions, resulting in an average completion time of 22 minutes. The average survey length for the general population survey was 18 minutes. The survey was in field from September 21 to October 7, 2021.

It is through the above survey, our in-depth interviews with patients and clinicians, and our 20+ years of ongoing collective efforts of direct engagement with patients and representing the lived experiences of the patient community that we provided through our patient group submission.

Time and time again the patients we survey and spoke to had aligned experiences of "sleep is a major factor in mood disorders, and getting enough sleep is very important for wellness maintenance. There was a solid understanding on the connection between mental health and sleep. Our survey results show has an impact on most physical and mental functions".

Survey respondents who identified as having experienced insomnia during the past year (n=673-676) were asked extra questions about sleep medication and treatments. One quarter of respondents are clearly dissatisfied. More than one quarter of respondents have used prescribed medication in the past to help with their sleep. Past usage of such medication is far more common among those who have been diagnosed with a sleep disorder (57%), people who have experienced insomnia (39%) and those with a mental health diagnosis (62%).

62% report having taken prescribed sleeping medication in the past two weeks, either at least three times a week (35%), once or twice a week (17%), or less than once a week (10%). Respondents who have received a sleep disorder diagnosis are more likely to have taken prescribed sleep medication in the past two weeks with 81% responding affirmative.

On average, the longest period of time that respondents have been using prescribed sleep medications at least three times a week was 59 months (nearly five years). Respondents who have taken prescribed sleep medication mostly saw a positive impact on their sleep from taking these medications and to a lesser extent, on their mental health.

In a separate MDSC national mental health survey conducted in September, 2021, 45% of respondents identified Improving Access to Medications and Treatment as their number 1 election issue for the Government of Canada, with 94% of them identifying it as important. It was the number one priority specified by respondents.

Our read of this is that the above does not state that they want to *patients expressed concern about being able to manage their sleep problems without becoming dependent on pharmacological treatments for insomnia.* It is saying patients are seeing positive impacts on their sleep, but they want to have choices for treatments, and they need to have access to these treatments. Choice + Access.

In our view, we strongly believe this reflects the majority of patients' perspectives and experiences.

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 patient group submission, we were very thorough in detailing how accessing the right treatments and having the ability to change to other treatments if a person finds their efficacies waning or, if longer-term use of one particular treatment leads to increase tolerance levels. It is beneficial to increase patient access to, and choice of, medications.

In our MDSC national mental health survey conducted in September of 2021, 45% of respondents identified improving access to medications and treatment as their number 1 election issue for the Government of Canada, with 94% of them identifying it as important.

MDSC believes that within these recommendations, there could have been more weight put on the patient group submissions, primarily around patient experiences, the importance of sleep and the negative impact lack of restorative sleep has on the lives of the patients, and the priority placed on choice and access considerations.

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.

It is therefore our belief that patient needs are not being met in regards to the choice and coverage of treatments for insomnia. The value and the benefit for patients in having a new treatment available for Canadians through Lemborexant cannot be under-emphasized.

When you look at the budget implications, we are consistently hopeful that within these deliberations CADTH would also have experts to weigh in on considering the implications of not providing additional treatments to combat insomnia,

In a recent major sleep study by Casper and Gallup to study sleep quality, sleep-related behaviors and the importance of sleep among American adults. The survey was conducted by web Jan. 11-17, 2022, with 3,035 adults, aged 18 and older, living in all 50 U.S. states and the District of Columbia, using the Gallup Panel. The American economy loses an estimated $44.6 billion annually in unplanned absenteeism as a result of poor sleep among workers. There are many other similar research studies who have all indicated there is a direct cost to our GDP due to presenteeism caused by poor sleep. So when we are only looking at the costs associated with covering these medications, we should also balance considerations with the connections with societal costs of not covering these medications.

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.

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.
Currently, it is not recommending reimbursements conditions, we hope you reconsider this.

[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.
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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.

A. Patient Group Information	
Name	*Dave Gallson*
Position	*National Executive Director*
Date	*26-08-2022*
☒	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.		
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**
Abbvie Inc	☐	☐	☒	☐
Janssen Inc	☐	☐	☒	☐
Pfizer Canada	☐	☐	☐	☒
Lundbeck Canada	☐	☐	☐	☒
Eisai	☐	☐	☒	☐
	☐	☐	☐	☐