Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

lemborexant (Dayvigo)

(Eisai Limited)

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

April 29, 2025

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

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Patient Input Template

Name of the Drug and Indication	**Lemborexant - Insomnia**
Name of the Patient Group	**Alzheimer Society of Ontario**
Author of the Submission	**Adam Morrison**

1. About Your Patient Group

The Alzheimer Society of Ontario (ASO) represents a federation of 26 frontline health and community support service providers, operating in every community across Ontario, and is part of a national federation of Alzheimer Societies across Canada. We supported over 84,000 clients last year, including both care partners and people living with dementia. We provide education and training to physicians and other health and social care professionals, as well as to the public, and work to reduce the stigma that is far too often associated with dementia. As a health service provider, ASO offers system navigation, care partner respite, adult day programs, therapeutic recreation, and more at little or no cost to families. With hundreds of staff and thousands of volunteers we seek to alleviate the personal and social consequences of Alzheimer's disease and related dementias, and to promote research into a cure. Learn more and find an Alzheimer Society near you: https://alzheimer.ca/on/en/about-us/find-your-local-alzheimer-society.

2. Information Gathering

Data were gathered anecdotally from the 26 local Societies of the Alzheimer Society of Ontario federation and synthesized by the Alzheimer Society of Ontario (coordinating agency).

References and population statistics were gathered from semi-structured conversations with participants of the Older Adult Insomnia Collaborative (including people with lived experience of insomnia, who also consulted their networks) and clinicians with expertise in older adult care.

A rapid literature scan of peer-reviewed and gray literature from organizations working in dementia, insomnia, and older adult care was also conducted to illustrate macro population characteristics and patient need.

3. Disease Experience

According to Ontario Health, in 2021 20% of the adult population in Ontario reported living with insomnia.[1] Using age breakdowns of the population, this amounts to roughly 2 million people who experience insomnia in the province.[2] Insomnia is therefore a highly prevalent condition in the population, with even higher rates in people living with dementia and their care partners.

Lower socioeconomic status has been associated with poorer sleep, including factors such as irregular work hours, living in noisy or unsafe environments, stress, health behaviours, and comorbidities.[3] [4] As such, insomnia and sleep disturbances present a health equity challenge, with populations at lower socioeconomic status having fewer options to address sleep challenges in their environments, including but not restricted to pharmacological and non-pharmacological interventions. A drug that is specifically targeted to treat insomnia, approved in Canada but not covered by public drug plans, compounds health inequities for people who are not able to pay out of pocket for this treatment.

Insomnia is associated with a higher risk of chronic conditions such as type 2 diabetes, cardiovascular disease, cognitive decline (including mild cognitive impairment and dementia), and cognitive disorders.[5] [6] [7] Many clients of the Alzheimer Society of Ontario live with multiple chronic conditions and seek support for dementia as well as associated conditions such as insomnia.

The Alzheimer Society of Ontario supported more than 84,000 clients last year. Insomnia is a common complaint raised by people living with dementia and their care partners in counselling programs, day programs, and social activation programs run by our local Societies and affiliated community service partners. Requests for support with insomnia are also common as reported by our First Link patient navigation service, where staff provide direct support and referrals to health and social care programs for dementia and associated conditions. Our clients report increased memory, orientation, and mobility/energy challenges related to sleep disturbances and insomnia.

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[1] Canadian Community Health Survey, Ontario Share File, 2021.
[2] Government of Ontario. Ontario Demographic Quarterly: highlights of second quarter. October 2024. https://www.ontario.ca/page/ontario-demographic-quarterly-highlights-second-quarter.
[3] Chaput JP, Tomfohr-Madsen LM, Carney CE, et al. Examining sleep characteristics in Canada through a diversity and equity lens. Sleep Health. 2024;10(3):316-20.
[4] Jehan S, Myers AK, Zizi F, et al. Sleep health disparity: the putative role of race, ethnicity and socioeconomic status. Sleep Med Disord. 2018;2(5):127-33.
[5] Johnson KA, Gordon CJ, Chapman JL, et al. The association of insomnia disorder characterised by objective short sleep duration with hypertension, diabetes and body mass index: a systematic review and meta-analysis. Sleep Med Rev. 2021;59:101456.
[6] Sofi F, Cesari F, Casini A, Macchi C, Abbate R, Gensini GF. Insomnia and risk of cardiovascular disease: a meta-analysis. Eur J Prev Cardiol. 2014;21(1):57-64.
[7] Xu W, Tan CC, Zou JJ, Cao XP, Tan L. Sleep problems and risk of all-cause cognitive decline or dementia: an updated systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2020;91(3):236-44.

4. Experiences With Currently Available Treatments

Cognitive Behavioural Therapy for Insomnia

Ontario Health released the Quality Standard on Insomnia in 2025, with five recommendations for how insomnia should be screened, assessed, treated, and managed.[8] In their quality standard and technical specifications document, Ontario Health states that cognitive behavioural therapy for insomnia (CBT-I) is the first-line treatment for insomnia. This therapy is cited as the gold standard by multiple national and international bodies with expertise in sleep research and treatment – it is effective in reducing insomnia, low cost, can be offered by many different clinicians in multiple modalities, and it is adaptable to patient needs. However, it is difficult to access.

While CBT-I is recommended as a first-line treatment for insomnia, access to care is limited in Ontario. There are financial barriers to CBT-I,[9] [10] including but not restricted to the therapy not being covered by public insurance. Few clinicians are aware of this therapy (for example, a 2019 online survey of clinicians in the United States and Canada found that over 40% felt unprepared to treat insomnia disorder),[11] and even fewer practice it (the same survey found that only 17% of clinical psychologists in the United States and Canada offered CBT-I). In essence, there is a reliable course of therapy that should be used as a first-line treatment, but it is not well-known, readily available, nor covered by public health plans.

In discussions with the lived experience advisors on the Older Adult Insomnia Collaborative, none of them had heard of CBT-I until they joined the group and heard about this treatment from clinician members of the group. All four of the lived experience advisors in this group had experienced insomnia for 20+ years, raised their symptoms with their primary care providers multiple times, and had never been educated about or referred for CBT-I. In follow-up conversations with the lived experience advisors, they also stated that only one person in their networks they reached out to had heard about CBT-I, and she was provided a website and told that it was nearly impossible to find a clinician who offered the service in her region.

Insomnia and Dementia

Sleep disturbances (including insomnia) and dementia have a bi-directional relationship: people with sleep disturbances are more likely to develop dementia, and people living

[8] Ontario Health. Quality Standards: Insomnia Disorder – Technical Specifications. February 2025.https://www.hqontario.ca/Portals/0/documents/evidence/quality-standards/qs-insomnia-disorder-technical-specifications-en.pdf
[9] Morin CM. Cognitive behavioural therapy for insomnia (CBTi): from randomized controlled trials to practice guidelines to implementation in clinical practice. J Sleep Res. 2020;29:e13017.
[10] Ontario Health. Insomnia Disorder Quality Standard Advisory Committee and public feedback. 2024.
[11] Zhou ES, Mazzenga M, Gordillo ML, Meltzer LJ, Long KA. Sleep education and training among practicing clinical psychologists in the United States and Canada. Behav Sleep Med. 2021;19(6):744-53.

with dementia have a high prevalence of sleep disturbances (i.e. 20% have clinically-significant disturbances and 38% have any sleep disturbance).[12] [13] [14] [15] Studies also indicate that 50-67% of care partners of people living with dementia experience sleep disturbances, including insomnia.[16]

Insomnia is a highly prevalent comorbid condition with dementia, and current sedative medications are associated with higher risks and harms to our clients. CBT-I, while recommended as a first-line treatment for adults, is a behavioural intervention, and not typically offered to people living with dementia due to the inability of people with cognitive decline to commit to sustained behavioural change. There are some early trials offering CBT-I to people living with dementia and their care partners as a dyad,[17] [18] but these are small interventions and early in their research trajectory.

Until research and implementation of CBT-I for people living with dementia and their care partners advances, many of our clients have no alternative to treating their insomnia besides pharmacotherapy. Even if this promising research develops into new protocols for therapeutic treatment, there are significant barriers to education, training, and offering CBT-I with the lack of providers and cost barriers to taking the therapy.

The current practice of prescribing sedatives off-label to treat insomnia over the long term is associated with harm in the general population, which increases for older adults and those living with comorbid conditions such as dementia and frailty. Many of our clients find themselves in a difficult situation:

- They cannot access the recommended first-line intervention to treat their insomnia (i.e. CBT-I) because of their dementia;
- They are not informed about appropriate medications to treat their condition (i.e. dual orexin receptor antagonists like Lemborexant) because of lack of provider knowledge, so they are prescribed inappropriate medications that may cause additional harm; and
- Even if they do learn about potentially appropriate medications like Lemborexant, they experience financial barriers that prohibit them from taking the clinically appropriate pharmacotherapy to treat their insomnia.

[12] Irwin et al. Lancet Neurol. 2019;18(3). doi:10.1016/S1474-4422(18)30450-2.
[13] Krause et al. The sleep-deprived human brain. Nat Rev Neurosci. 2017;18(7).
[14] Diem et al. American Journal of Geriatric Psychiatry. 2016;24(3).
[15] Webster Sleep. 2020;43(4). doi:10.1093/sleep/zsz251.
[16] McCurry SM, et al. Sleep Disturbances in Caregivers of Persons with Dementia: Contributing factors and treatment implications. Sleep Med Rev. 2007. https://pmc.ncbi.nlm.nih.gov/articles/PMC1861844/.
[17] Song et al. Disabil Rehabil. 2021;43(13).
[18] Song et al Journal of the American Geriatrics Society. 2024;72(4):1207-1215.

Pharmacotherapy

All the lived experience advisors on the Older Adult Insomnia Collaborative regularly take medications for sleep prescribed by their primary care provider. This was consistent with people in their networks with insomnia whom they consulted to ask about their experiences. Anecdotally, there is a high number of older adults living with insomnia and sleep disturbances who take at least one prescription medication off-label to manage their condition.

Pharmacotherapy for insomnia consists primarily of off-label use of sedatives to manage sleep. In 2023, 10% of 18–35-year-olds were taking a prescription medication for sleep, rising to 25% for people age 65 and older.[19] Many older adults are prescribed benzodiazepines, non-benzodiazepine sleep medications, and barbiturates to manage their insomnia. They are also prescribed anti-depressants and anti-psychotics off-label to manage insomnia. These medications are associated with a risk of adverse drug reactions and harmful side effects, especially for older adults taking multiple prescription medications and living with multiple chronic conditions. One study found 83% of people with insomnia also had comorbid conditions, and one in four older adults had four or more comorbidities.[20]

In a meta-analysis of 24 studies, sedative hypnotics prescribed to older adults for treating insomnia were linked to a higher incidence of cognitive impairment, a higher risk of falls,[21] and a higher risk of motor vehicle crashes.[22] These medications are also linked to hospitalizations,[23] where older adults, and especially people living with dementia, are subjected to additional risk of harm during their hospital stay due to the model of care and the unfamiliar environment.

Clients of the Alzheimer Society frequently state their fear of being hospitalized, with an assumption that they will be admitted for a long stay and possibly designated as alternate level of care bound for long-term care. Some are reluctant to take sedatives prescribed to them when they are also told about the risk of falls and related harms, which could lead to premature institutionalization. Alzheimer Society staff frequently hear a mix of skepticism about taking off-label prescriptions for sleep mixed with desperation for any solution that might help with their condition.

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[19] Morin CM, et al. Prevalence of Insomnia and Use of Sleep Aids Among Adults in Canada. Sleep Med. 2024 Dec:124:338-345.
[20] Foley, D.; Ancoli-Israel, S.; Britz, P.; Walsh, J. *Journal of Psychosomatic Research* 2004, *56* (5), 497–502.
[21] Amari DT, Juday T, Frech FH, Wang W, Wu Z, Atkins N Jr, Wickwire EM. Falls, healthcare resources and costs in older adults with insomnia treated with zolpidem, trazodone, or benzodiazepines. BMC Geriatr. 2022 Jun 4;22(1):484
[22] Glass J, et al. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits *BMJ* 2005; 331 :1169
[23] Chalet FX, Saskin P, Ahuja A, Thompson J, Olopoenia A, Modi K, Morin CM, Wickwire EM. The Associations between Insomnia Severity and Health Outcomes in the United States. J Clin Med. 2023 Mar 22;12(6):2438.

Cost if often cited as a barrier to taking medications like Lemborexant, which is not currently covered under public drug plans. Clients report that they would be more likely to switch to a safer medication to treat their insomnia but for out-of-pocket costs for medications not covered.

5. Improved Outcomes

In Canada in 2021, the economic impact of insomnia in relation to people living with comorbid chronic conditions (such as dementia and frailty) was estimated to be $1.9 billion – including direct health care costs and indirect costs in the workforce.[24] A 5% reduction in insomnia symptoms in the population would save at least $353 million per year.[25] Therefore, a medication like Lemborexant, designed to treat insomnia with fewer side effects than medications presently used off-label and for longer than indicated, could provide significant cost savings to the health system.

The high prevalence of inappropriate medications usage in insomnia raises serious safety concerns for patients suffering from insomnia, particularly older adults living with dementia. The rate of falls and hospitalizations, linked to current prescription medications used for sleep, could be reduced by gradually switching appropriate patients to dual orexin receptor antagonists (DORAs). This would improve quality of life for people living with dementia, reduce burnout of their care partners, reduce unnecessary emergency department visits, reduce long hospital admissions, and delay the expression of need for long-term care.

While there is presently a low level of education about medication options for insomnia, particularly DORAs such as Lemborexant, lived experience advisors on the Older Adult Insomnia Collaborative suggested that access to these medications could be a 'game changer.' They expressed hopelessness about their dependence on sedatives prescribed off-label for their condition, citing a 'dark cloud' of poor sleep and low energy during wakefulness that persists for decades.

Lived experience advisors, in conversations with their networks, note a lack of awareness about medications designed specifically to treat insomnia. This highlights an unmet need for better education regarding current guidelines and more effective and safer treatment options. When raised in conversation, lived experience advisors noted optimism and hopefulness that their insomnia could be treated appropriately, that they could live at a higher level of function during the day, and dedicate more time to living well in the community.

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[24] Chaput JP, Janssen I, Sampasa-Kanyinga H, et al. Economic burden of insomnia symptoms in Canada. Sleep Health. 2023;9(2):185-9.
[25] Hafner M, Romanelli RJ, Yerushalmi E, Troxel WM. The societal and economic burden of insomnia in adults: an international study [Internet]. Santa Monica (CA): RAND Corporation; 2023 [cited 2024 Dec 13]. www.rand.org/pubs/research_reports/RRA2166-1.html.

6. Experience With Drug Under Review

The Alzheimer Society of Ontario did not conduct focus groups specifically on Lemborexant, though staff frequently refer patients to their primary care providers to talk about their sleep disturbances. Anecdotally, many of our clients living with dementia and insomnia would switch to a drug tailored to treat insomnia when they learn about it. They put a very high value on improved quality of life, sleep, and social interaction with their friends and families as the result of appropriate treatment of their insomnia.

7. Companion Diagnostic Test

Not applicable; this drug can be prescribed without a companion diagnostic test. Ontario Health's Quality Standard on Insomnia recommends clinicians conduct a sleep history, an insomnia assessment tool (such as the Insomnia Severity Index), along with physical and mental health histories to fully understand the patient's level of insomnia and needs before offering a course of treatment, including but not exclusive to pharmacotherapy.[26]

8. Anything Else?

The Alzheimer Society of Ontario is strongly supportive of a positive review of Lemborexant for coverage under public drug plans to improve the health of our population and reduce inequities to accessing treatment. The safety of the drug has already been confirmed by Canada's Drug Agency and may provide relief to the significant number of people living with dementia who also have insomnia. Our clients are not considered eligible for the currently available treatment (i.e. CBT-I), and the practice of prescribing sedatives off-label is a poor status quo that puts our clients at high risk for multiple harms while not managing their underlying insomnia or symptoms.

[26] Ontario Health. Quality Standards: Insomnia Disorder – Care for Adults. February 2025. https://www.hqontario.ca/portals/0/documents/evidence/quality-standards/qs-insomnia-disorder-en.pdf

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CDA-AMC may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No – this submission was drafted by Alzheimer Society of Ontario staff.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No – this submission was researched and prepared by Alzheimer Society of Ontario staff.

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 Canada (funds provided for dementia care advocacy, not insomnia or Lemborexant)				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.

Name: Adam Morrison
Position: Senior Director, Public Policy & Partnerships
Patient Group: Alzheimer Society of Ontario
Date: 29 April 2025

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Patient Input Template

Name of the Drug and Indication	**Dayvigo (lemborexant) - Chronic Insomnia**
Name of the Patient Group	**Migraine Canada**
Author of the Submission	**Wendy Gerhart**

1. About Your Patient Group

Migraine Canada is a national, federally registered charity founded in late 2018. Our mission is to provide education, support, and raise awareness about the impact of migraine. We advocate for optimal care for people living with migraine and promote research toward a cure.

With the support of dedicated clinicians, contributors, and our community, Migraine Canada delivers evidence-based, up-to-date information on migraine disease and treatment to Canadians, including patients, caregivers, and healthcare professionals. We create and share educational resources that reflect the latest in migraine research and care.

Through our website, social media channels, and online forums, we drive awareness and community engagement. Our growing community includes over 7,000 email subscribers and several thousand members engaging through our social media channels (Facebook, IG, YouTube, LinkedIn, BlueSky)

Website (English): www.migrainecanada.org

2. Information Gathering

Canada's Drug Agency (CDA-AMC) is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

The information provided in this submission was collected through three surveys. In late fall of 2021, we launched a Quality-of-Life online survey. It was promoted across Canada through Migraine Canada's digital and social media channels. In total, 1,165 Canadian adults with migraine and their caregivers responded to the online survey. Of our total respondents, 19% live with low frequency migraine, 28% live with 8-14 days / month with migraine and 52% live with chronic migraine 15 or mores days. The spectrum of representation was national with the majority (68%) participating between the age of 30-59.

In March 2022, Migraine Canada launched a national online survey to gather additional insights on sleep to seek input from patients with experience on Dayvigo (lemborexant). It was promoted across Canada through Migraine Canada's digital and social media channels with promotion. In

total, 220 Canadians with migraine responded to the survey related directly to insomnia. Of our total respondents, 91% were female and 9% male. Similar to the quality-of-life survey, the majority of patients were between the age of 30-59 (69%).

In the fall of 2024, an additional survey was launched with a total of 177 respondents who live with migraine and experience sleep issues/insomnia.

The most recent survey (fall of 2024), was also promoted across Canada through Migraine Canada's digital and social media channels with promotion. In total, 177 Canadians with migraine responded to the survey related directly to insomnia. We had 20 respondents who have experience on Dayvigo.

In the most recent survey, close to 25% live with episodic migraine, and 72% live with chronic migraine (15 or more days). The majority (93%) were female and the spectrum of representation was national with the majority (68%) participating between the age of 30-59. The demographics were similar to the quality-of-life survey, the majority of patients were between the age of 30-59 (69%).

The sleep survey launched this fall intended to identify the various sleep disruption profiles in individuals living with migraine, highlight how sleep issues are thought to affect every day functioning, and determine the perceived efficacy of different sleep remedies and treatments.

Insomnia is a common co-existing complication for people living with migraine, regardless of whether they have been formally diagnosed with a sleep disorder (insomnia) or not. Close to 30% of respondents who completed the survey have received a diagnosis of insomnia by a healthcare professional while 70% have sleep issues nightly (47%) or 3 or more times per week (46%) for more than 3 months (the definition of insomnia was provided).

3. Disease Experience

CDA-AMC involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

Migraine is not just a headache — it is a complex neurological disease.
It affects over 1 billion people worldwide and in Canada roughly 1 in 4 individuals. While migraine is most common between the ages of 25 and 55, it can impact people of all ages, including 10% of children. It affects women three times more often than men, impacting 25% of women and 8% of men globally.

Migraine is classified by the frequency of attacks:

- **Episodic Migraine** affects fewer than 15 days per month. About 12% of adults with migraine fall into this group, which is further divided into low-frequency (1–6 days/month) and high-frequency (7–14 days/month) categories.
- **Chronic Migraine** occurs 15 or more days per month and affects about 2% of adults with migraine. Chronic migraine is linked to greater disability, increased comorbidities, and a higher risk of developing medication overuse headache (MOH) — a condition caused by frequent use of acute treatments that paradoxically worsens headaches.

Migraine symptoms often include severe, throbbing, recurring head pain (on one or both sides), nausea, vomiting, dizziness, and heightened sensitivity to light, sound, touch, and smell. About 25% of people with migraine experience aura — temporary neurological disturbances such as visual changes, speech difficulty, or numbness — typically lasting less than an hour.

There are two primary phases of migraine life:

- **Ictal phase (during an attack):** Migraine attacks disrupt daily life, often causing people to withdraw to a dark, quiet space. Severe pain, sensory hypersensitivities, nausea, vomiting, and cognitive difficulties (such as trouble concentrating or speaking) can severely impair work, social interaction, and basic functioning.
- **Interictal phase (between attacks):** Even between attacks, individuals may experience anxiety about future episodes and reduced cognitive function.

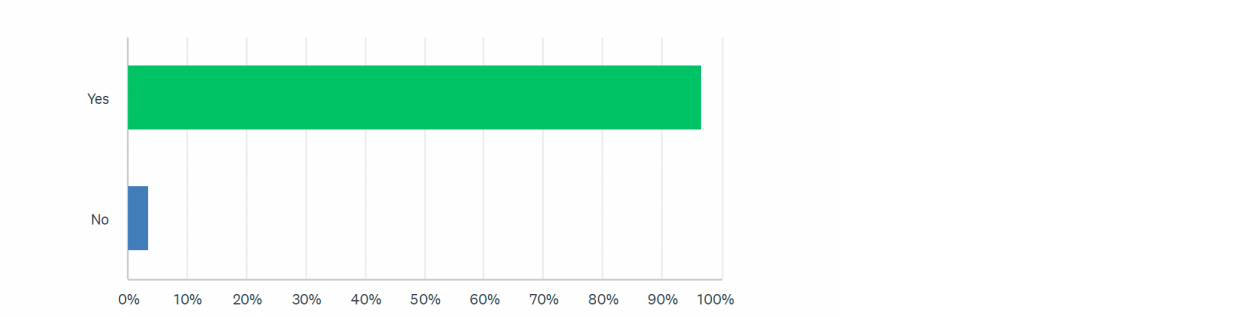
While a well-managed migraine attack may be brief, uncontrolled migraines can last for days, severely impacting quality of life.

Impact on Sleep – The data provided below is summarized from the fall 2024 survey on sleep:

The table below demonstrates how often people have issues with their sleep.

	NEVER OR RARELY	1-2 TIMES PER WEEK	3-6 TIMES PER WEEK	NIGHTLY
Difficulty falling asleep	18.75% 33	28.41% 50	27.84% 49	25.00% 44
Difficulty staying asleep	7.51% 13	19.65% 34	34.10% 59	38.73% 67
Early morning waking with inability to return to sleep	20.83% 35	29.17% 49	29.17% 49	20.83% 35
Difficulty functioning the following day	9.88% 17	30.81% 53	41.86% 72	17.44% 30

As noted above, when asked if respondents experienced the symptoms above for more than 3 months, the majority, 97% indicated yes.



When asked how insomnia/sleep issues impacted quality of life, we can assume from the data outlined below, that most people regularly or are impacted all the time is fairly significant.

	NEVER	SOMETIMES	REGULARLY	ALL THE TIME
Household responsibilities	4.29% 7	47.85% 78	36.81% 60	11.04% 18
Performance and/or attendance at work	16.46% 26	47.47% 75	23.42% 37	12.66% 20
Family time/parenting/caregiving	13.75% 22	52.50% 84	26.88% 43	6.88% 11
Engaging in physical exercise	3.66% 6	37.20% 61	40.24% 66	18.90% 31
Eating habits	14.72% 24	47.24% 77	27.61% 45	10.43% 17
Cognitive function (focus, attention, memory)	2.42% 4	37.58% 62	38.18% 63	21.82% 36
Partner relationships/intimacy	16.15% 26	45.34% 73	27.33% 44	11.18% 18
Social interactions	6.79% 11	48.15% 78	34.57% 56	10.49% 17
Mood	2.44% 4	37.80% 62	42.07% 69	17.68% 29
Energy level	1.21% 2	22.42% 37	42.42% 70	33.94% 56

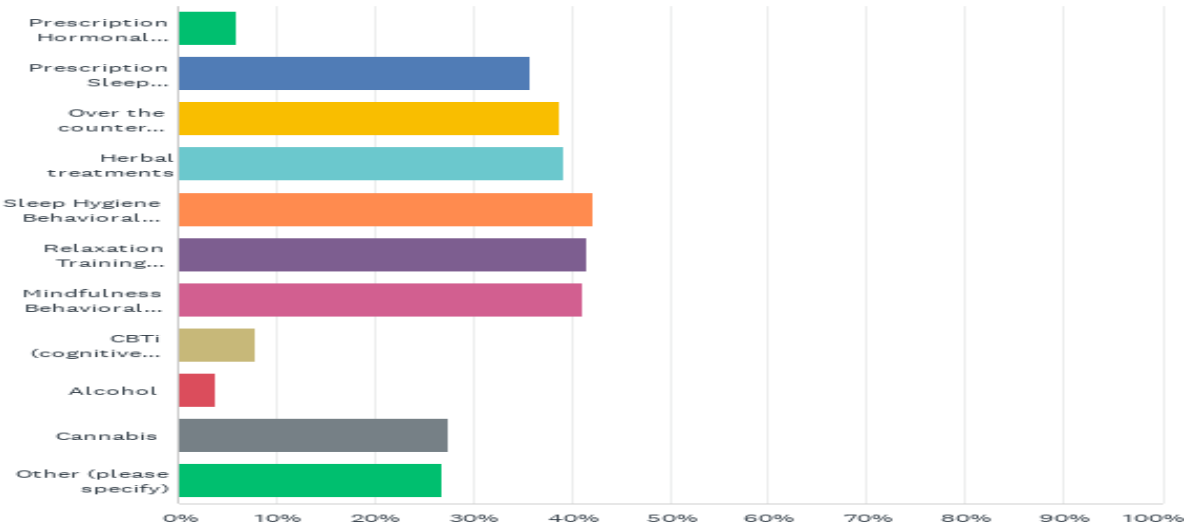
4. Experiences With Currently Available Treatments

CDA-AMC examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

Patients have tried a number of different treatments and remedies to help with their sleep issues. Over 42% have tried sleep hygiene behavioural therapies, followed by relaxation and mindfulness. Following non pharmacologic intervention, close to 40% have tried over the counter and prescription medications.

What have you tried to improve your sleep and insomnia?
(check all that apply)



The majority (60%) of patients are not satisfied with how they currently manage their insomnia/sleep issues.

Patient testimonials:

> *"Gabapentine prescription. Discontinued, too many side effects".*
>
> *"Tried amitriptyline for two years, helped sleep but not the migraines".*
>
> *"Amytriptaline for 18 months helped but I gained quite a bit of weight. Beyond that nothing but the obvious – don't drink caffeine, get fresh air, exercise, medication. Nothing helps".*
>
> *"Tried a few different medications but they made things worse".*
>
> *"I was prescribed medication but it left me feeling groggy so I stopped taking it".*
>
> *"My doctor won't prescribe me anything because everything that works for people is addicting. So I suffer with no sleep and migraine".*
>
> *"A couple of the prescribed medications I've tried made feel so horrible the next day. Its like an out of body experience. Helped my sleep but side effects were to much. At least feeling absolutely exhausted is better than feeling spacey and out of it".*
>
> *"I take prescription sleeping pills nightly and take stimulant every morning".*
>
> *"Medication/meditation. Medication made me very groggy throughout the next day as I'm very sensitive".*

5. Improved Outcomes

CDA-AMC is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers,

and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

Overall, many patients have not found an over-the-counter or prescription medication that effectively manages their sleep issues. A common concern is that the side effects of available treatments often lead to discontinuation and / or fear of addiction. A top priority for people living with migraine related to sleep is to find treatment that can improve their sleep and potentially reduce the frequency and intensity of their migraine attacks.

Sleep is a critical component in managing migraine. Clinicians emphasize the importance of lifestyle modifications — often summarized by the acronym SEEDS (Sleep, Exercise, Eat, Diary, Stress). Poor sleep can significantly affect tolerance, mental health, and cognitive function; in addition to the frequency and intensity of their migraine attacks.

Patients often compare living with migraine to being caught in a “washing machine” — with symptoms and challenges constantly swirling around. Gaining control over even one or two aspects, such as improving sleep, can make a noticeable difference. Better sleep can support improved mental health, provide more energy for exercise, encourage healthier eating, and contribute to improving health outcomes overall.

People living with migraine are desperate for better options to improve their quality of life. Being able to manage complications, like sleep disturbances, can reduce stress and anxiety — two factors that often worsen migraine. Treatments that improve sleep quality and duration, while minimizing daytime insomnia, would be highly valued.

There is also strong patient demand for medications that are non-addictive. Many physicians are cautious about prescribing current options, and many patients are reluctant to take them due to concerns about dependency. In addition to safety, patients seek treatments with fewer side effects, such as reduced drowsiness or cognitive impairment. Long-term effectiveness is another key need, as many existing treatments lose their effectiveness over time.

When asked what success with a new medication would look like, respondent said:

> *“Waking up feeling rested.”*
>
> *“Sleeping through the night with no hangover and no weight gain at least 5 nights a week.”*
>
> *“Be less tired all the time. Have more energy. I probably would hurt less and be a more productive human being with a positive attitude.”*
>
> *“Occasional sleep issues would be success, but of course having no sleep issues would be optimal. That’s hard to imagine though. It would be so uplifting to wake up fully rested and ready to tackle the day instead of triggering a migraine and struggling through the day.”*
>
> *“Decreased anxiety and depression, less irritability, more energy, desire and ability to go out more, exercise tolerance, ability to socialize more, ability to do more than the absolute minimum of housework and shopping.”*

"Freedom to live my life, make plans, less stress & anxiety. It would give me many more hours a day of life, instead of wasting time in bed, unable to sleep or unable to wake up from the hangover caused by meds/supplements."

"Success would be falling asleep with ease, and having quality sleep for the 8-9 hrs a night I need, waking up feeling rested and having the energy and capacity to fully show up in my life."

The options in this new class (DORA) of medications to manage insomnia bring hope to Canadians and should be accessible.

6. Experience With Drug Under Review

CDA-AMC will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways? If applicable, please provide the sequencing of therapies that patients would have used prior to and after in relation to the new drug under review. Please also include a summary statement of the key values that are important to patients and caregivers with respect to the drug under review.

Information collected from our fall survey, reported that the non-prescription treatments include 6% of respondents reported using alcohol and 27% reported using cannabis as OTC remedies to improve their sleep and insomnia. Other OTC's respondents reported: melatonin (80%), Benadryl (30%), Valerian (17%), L-Tryptohan (11%), other: Zzzquil, magnesium ashwaganda, Gravol (30%).

Respondents reported using the following prescription medications: zopiclone (Imovane) (27%), trazadone (27%), gabapentin (24%). benzos (17%), lemborexant (Dayvigo) (9%), flurazepam (2%), temazepam (2%), ,zolpidem (Sublinxo) (8%), exzopiclone (Lunesta) (2%), triazolam (1%), DORA (1%), daridorexant (Quviviq) (1%), quetiapine (12%), mirtazapine (5%), pregabalin (6%), other: unknown name, Avantil for migraines, clonzaempam + amitriptyline, Xyrem, cyclobenzaprine, others included prazosin, clonidine, sertraline, anxiety meds, Concerta, propranolol, tryptophan, Stamoc, lorzaepam, prazosin (29%).

Some comments include:

"Its probably listed, I just remember if tasted like pennies and didn't help much".

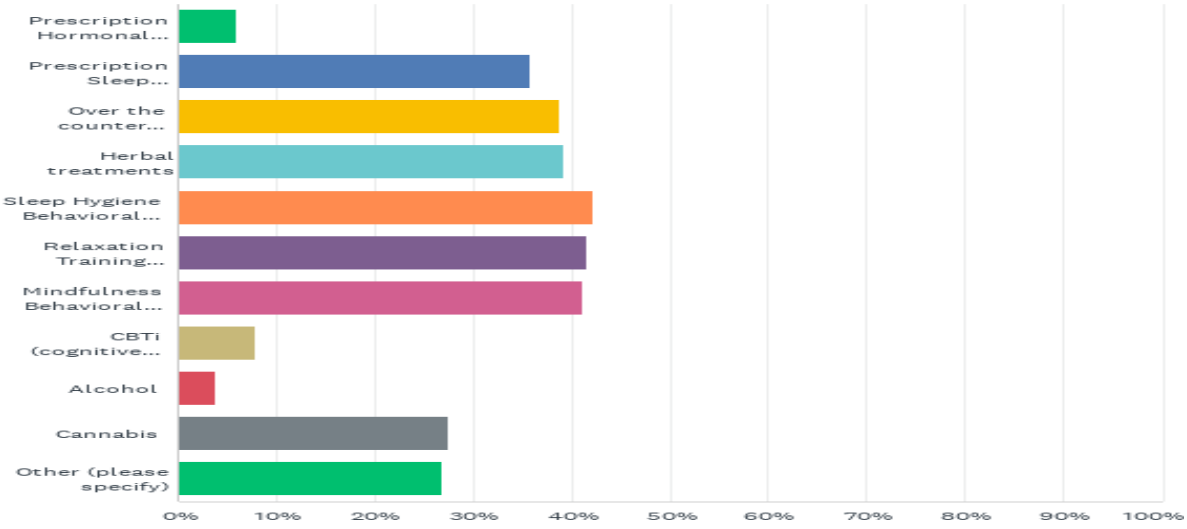
"A few but I'm not completely sure which of these".

"Have tried many more over the years but with my stroke I just can't remember all of them very sorry".

When asked about what over the counter medications respondents have tried, melatonin was used the most (82%), followed by Benadryl (34%), Valerian (21%) and Cannabis (28%). Other treatments not offered as a selection included several OTC sleep options (NyQuil, Advil PM, etc), gravol, essential oils etc.

Patients have tried a number of different treatments and remedies. Over 42% have tried sleep hygiene behavioural therapies, followed by relaxation and mindfulness. Following non pharmacologic intervention, close to 40% have tried over the counter and prescription medications.

What have you tried to improve your sleep and insomnia?
(check all that apply)



The majority (60%) of patients are not satisfied with how they currently manage their insomnia/sleep issues.

Patient testimonials:

> *"Gabapentine prescription. Discontinued, too many side effects".*
>
> *"Tried amitriptyline for two years, helped sleep but not the migraines".*
>
> *"Amytriptaline for 18 months helped but I gained quite a bit of weight. Beyond that nothing but the obvious – don't drink caffeine, get fresh air, exercise, medication. Nothing helps".*
>
> *"Tried a few different medications but they made things worse".*
>
> *"I was prescribed medication but it left me feeling groggy so I stopped taking it".*
>
> *"My doctor won't prescribe me anything because everything that works for people is addicting. So I suffer with no sleep and migraine".*
>
> *"A couple of the prescribed medications I've tried made feel so horrible the next day. Its like an out of body experience. Helped my sleep but side effects were to much. At least feeling absolutely exhausted is better than feeling spacey and out of it".*

“I take prescription sleeping pills nightly and take stimulant every morning”.

“Medication/meditation. Medication made me very groggy throughout the next day as I’m very sensitive”.

In summary, when speaking with patients, people prefer to manage most conditions naturally or by behavioural changes (ie. sleep hygiene, less screen time, meditation, etc). When conditions become chronic and are affecting day to day activities, people then turn to either over the counter treatments or prescription. Most of the older medications prescribed to treat insomnia either don’t work or have intolerable side effects or are addictive.

As previously mentioned, only 30% of respondents feel their current treatment for insomnia is acceptable.

In the survey launched this fall, to date we had 20 participants with experience on Dayvigo. Approximiately 60% of patients experienced some or significant improvement in their sleep/insomnia from Dayvigo compared to previous treatments they have used.

When asked about side effects, 50% of respondents reported no side effects, while 20% reported having some side effects, which included nightmares. Fifty percent of these respondents said the medication was tolerable and they continued to take it; while 15% said they needed to stop taking the medication, including one respondent who said they could not afford to pay for the medication.

When asked how people accessed Dayvigo, 57% reported having accessed it with private coverage, 5% reported receiving a sample from a healthcare provider and 29% paid out-of-pocket.

It is important to highlight, Dayvigo is safer option to what is currently available. There is less risk of becoming dependent compared to other less optimal options currently available. The possibility of safe, effective and tolerable treatment to resolve sleep issues supports our request to have Dayvigo widely accessible to people living in Quebec.

Testimonials about the disadvantages and advantages of Dayvigo included:

“Dayvigo is a good option for me. I’m not sleep eating, not as sedated and can safely get up during the night and function the next day”.

“Didn’t work as well as zopliclone but I know it’s a better/safer option”.

“It helped regulate my sleep pattern and eliminate the stress of the insomnia”.

“It helped significantly. I am able to fall asleep where I couldn’t have before”.

“Dayvigo is the best thing that has happened to me. No groggy/brain fog side effects. Been on it for two years now”.

“Dayvigo has helped my sleep immensely.”

“Discussed [with physician] and tried Dayvigo, this has brought significant improvement”.

"Dayvigo worked very quickly and without the side effects of other medications I've tried".

"Dayvigo worked quickly to help sleep and didn't make me feel groggy the next day and felt awake, alert and productive"

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

N/A

8. Anything Else?

Is there anything else specifically related to this drug review that CDA-AMC should know?

There remains a significant unmet need in the treatment of chronic insomnia. New treatment options offer hope and the opportunity to change the trajectory of a patient's health journey. People living with migraine often experience multiple co-morbidities, including depression, anxiety, and sleep disturbances. Addressing even one of these conditions could have a profound positive impact on other aspects of their health.

Patients with migraine already face limited treatment choices that must balance efficacy, tolerability, and safety. This highlights the urgent need for newer, safer options that align with patients' needs and personal goals, especially to manage co-existing conditions like insomnia. Current therapies, such as benzodiazepines and Z-drugs, are associated with risks of dependency, poor tolerance, and cognitive side effects. While behavioral therapies like CBT-I are proven effective, they remain largely inaccessible for many patients.

It is an ethical imperative to address disparities in access to effective treatments. Patients with lower socioeconomic status or those living in remote areas often face additional barriers to care,

resulting in inequitable health outcomes. Treatment gaps caused by cost, inadequate funding, and geographic barriers unfairly limit access for vulnerable populations.

The societal burden of insomnia is substantial, impacting economic productivity through increased healthcare costs, lost workdays, and heightened accident risk due to sleep deprivation. Poor sleep is estimated to cost the Canadian economy approximately $44.6 billion annually in unplanned absenteeism alone. Studies consistently demonstrate the negative impact on GDP, driven primarily by presenteeism. Additional societal costs include hospitalizations, untreated comorbidities, repeated healthcare visits, lost wages, and decreased participation in social and economic activities.

In summary, the information presented clearly illustrates the urgent need for Canadians to have equitable access to affordable, innovative treatments for chronic insomnia, including new options like Dayvigo. Existing therapies often have intolerable side effects or addiction risks, discouraging both clinicians from prescribing and patients from using them.

We strongly urge the Canadian Drug Agency (CDA) to issue a positive recommendation for Dayvigo for the treatment of chronic insomnia. Medications in this new class offer a promising balance of improved sleep outcomes and enhanced safety profiles. A positive recommendation for Dayvigo would provide a much-needed solution — restoring quality of life for some and offering meaningful relief for many others, ultimately improving health outcomes across Canada.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CDA-AMC may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   This submission was summarized and written solely by the staff at Migraine Canada, free from consultation, advice, influence or financial support from any outside individual, group or company.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   Migraine Canada worked with a third party to create the on-line Quality of Life survey. Analysis was completed internally.

   Migraine Canada independently developed and analyzed the subsequent surveys on sleep.

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			X	
Idorsia	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.

Name: Wendy Gerhart
Position: Executive Director
Patient Group: Migraine Canada
Date: April 28, 2025

CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Dayvigo/lemborexant
Indication: For the treatment of insomnia in adults diagnosed according to the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) referring to chronic insomnia disorder (CID)
Name of Patient Group: Mood Disorders Society of Canada
Author of Submission: Dave Gallson

1. About Your Patient Group

Describe the purpose of your organization. Include a link to your website.

Mood Disorders Society of Canda (MDSC) is a leading national mental health organization, established in 2001, with a mission to provide individuals living with mental health challenges a cohesive, national voice. Our work spans advocacy, education, and support for patients and families affected by mood disorders and other mental health conditions, including insomnia. Through robust partnerships with stakeholders across public, private, and non-profit sectors, we have become a trusted resource in mental health advocacy. Our commitment to eliminating stigma and improving access to treatment aligns with the needs of the many Canadians who struggle with chronic insomnia and other sleep disorders.

With over 97,000 social media followers our vast mental health resources found on our various websites such as depressionhurts.ca, myMira.ca, CCMHN.ca, MDSC.ca and extensive engagement through our national mental health campaign, Defeat Depression, MDSC represents a powerful collective voice. We provide critical insights into the patient experience, advocate for improved access to care, and facilitate dialogue between patients and policymakers. Our online platforms and forums provide a space for individuals to share their lived experiences, making us uniquely positioned to speak on behalf of those affected by chronic insomnia.

Mood Disorders Society of Canada's Head Office is located at 46 Hope Crescent, Belleville ON K8P 4S2. A total of nine full time staff are in regions across Canada. Its main website is: MDSC.ca.

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

To complete this questionnaire, MDSC used a variety of methods, including sleep survey research, individual interviews with people who have insomnia and have tried/take other treatments, and individual interviews/one-on-one connections with people who have tried Dayvigo, as well as individual interviews with clinicians. MDSC also used data from a survey on insomnia and migraine, launched by Migraine Canada. More details regarding these data sources are noted below.

Patient-reported outcomes are fundamental in the evaluation of treatments for mental illnesses, including insomnia. MDSC collected valuable insights of real-world effectiveness of Dayvigo via surveys and engagement directly with patients who have used Dayvigo, including those with the co-diseases of sleep apnea, anxiety and depression. This type of data—capturing changes in sleep quality, daytime functioning, and overall well-being—is clinically meaningful in this disease area. Given that mental health conditions rely on patient experience as a primary measure of treatment success, findings of this nature are critical evidence in assessing the drug's value.

The data gathered from these sources highlights the urgent unmet need in the treatment of chronic insomnia and supports the case for the reimbursement of Dayvigo.

1. Sleep Survey Research

In 2021, MDSC conducted a comprehensive survey on sleep and mental health, involving over 1,200 Canadian participants (https://mdsc.ca/mood-disorders-society-of-canada-national-sleep-and-mental-health-survey). An online poll of 1,200 participants was randomly selected from throughout Canada to represent the general population. Furthermore, MDSC disseminated a survey link across its network, particularly on social media, which led to the completion of 49 additional surveys. Age, gender, and geographic quotas were used in the general population survey, and the survey's findings were also weighted according to those factors. The survey took place between September 21, 2021, and October 7, 2021.

The objectives of the sleep study were to better understand sleep habits, how sleep disorders such as insomnia affect our mental health, and how mental health concerns can also affect our sleep. MDSC contracted Narrative Research, an independent research company, to administer the survey and assess the findings.

The study aimed to identify the various sleep disruption profiles in individuals with and without mental health symptoms, highlight how sleep issues are thought to affect everyday functioning and mental health, identify the subjects that people are most interested in learning about re: sleep/insomnia (and their level of sleep expertise), and determine the application and perceived efficacy of different sleep remedies and treatments.

Insomnia was common among respondents, regardless of whether they have been diagnosed with a sleep disorder; over half (55%) report having had insomnia (and by definition chronic insomnia) in the previous year, with symptoms including trouble falling or staying asleep or waking up too early and not being able to go back to sleep. Ten percent (10%) of respondents said they have had a sleep problem diagnosis in the past from a medical expert. People who responded with chronic insomnia are more likely to be female and have annual household incomes under $50,000. Additional demographics of the 1,249 completed respondents:

Age: 16 to 29 - 13%, 30 to 49 - 39%, 50+ - 48%
Gender: Girl/Woman - 54%, Boy/Man - 45%
27% of respondents are retired, 44% employed, 9% employed part-time, 5% self-employed, 9% unemployed, with 3% currently identifying as students.
Income levels were:

Under $27,000 – 10%, $27,001 - $41,000 – 15%, $41,001 - $50,000 – 9%, $50,001- $100,000 – 36%, $101,000 or more – 22%, Prefer not to say - 8%

2. Engaging with PWLE and Clinicians

a) MDSC connected with one-on-one / interviewed 6 people who had direct experience taking Dayvigo; 3 did not provide their ages, the other three were in the following age ranges: 41-50, 51-60, and 61+.
b) MDSC also connected with two individuals that had experience with other medications (1 individual aged 60, and one aged 57).
c) We also had lengthy conversations with two clinicians - a family doctor and a psychiatrist.
d) Through our evaluation of patient and family member feedback, and remarks and experiences given through our MDSC online Discussion Forum (hosted on the MDSC website and serving as a platform for in-depth online discussions) we were able to gather additional experience and viewpoints.
e) Data and comments from a survey of patients with insomnia and migraine were also reviewed. In this survey, prepared by Migraine Canada's (n = 142), there were 12 people who reported having experience with Dayvigo. This survey was launched in 2024.

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

Chronic Insomnia: A Severe and Overlooked Burden

The following section draws heavily from our previous submissions to CDA-AMC and INESSS, as the experiences and unmet needs of individuals living with chronic insomnia remain largely unchanged. However, we wish to underscore several important points in this submission.

First, there is a critical distinction between insomnia and chronic insomnia from the patient perspective—while occasional sleeplessness is frustrating, patients with chronic insomnia described a debilitating condition that erodes a person's ability to live a normal life. It impacts physical (a 2024 report in *The Lancet* emphasized that lack of sufficient sleep is linked to cancer, chronic respiratory diseases, dementia, cardiometabolic disorders, and mental health conditions https://www.thelancet.com/journals/landia/article/PIIS2213-8587(24)00132-3/fulltext) and mental health, disrupts work or school productivity, strains relationships with partners, children, and friends, and creates significant societal costs. Despite this, patients reported that their chronic insomnia remains under-recognized and under-treated.

Further, while Cognitive Behavioural Therapy for Insomnia (CBTi) is recommended as the first-line treatment, many patients reported they weren't aware of it, many weren't always able to access it, and some patients reported it didn't work for them. As a result, many individuals turned to medication—but the data shows that these are often older drugs associated with dependency and side effects. Where medication is needed, patients deserve safer, more targeted options that do not create additional health burdens and risks. This section outlines these challenges in detail, emphasizing the urgency of addressing chronic insomnia as both a standalone mental illness, and as a critical factor in managing comorbid mental illnesses.

Chronic insomnia disrupts the lives of millions of Canadians, with 2–4 million individuals affected nationwide (https://www.statcan.gc.ca/o1/en/plus/1653-cant-sleep-count-sheep). This condition isn't just about poor sleep—it significantly impacts physical health, emotional well-being, and daily functioning. Left untreated, it increases the likelihood of severe health problems, including mood disorders, heart disease, metabolic conditions, substance misuse, and even suicide. Additionally, insomnia can shorten life expectancy and strain healthcare systems.

The broader societal effects are also staggering. Sleep deprivation increased workplace absenteeism, diminishes workplace performance, increases the risk of accidents, and lowers overall productivity, costing the economy billions every year. People with insomnia face not only impaired quality of life issues, but also heightened social isolation, creating a ripple effect of negative consequences for communities and healthcare providers alike.

- According to the results in MDSC's national survey on sleep and mental health, 66% of respondents said they couldn't shut off at night, and that not being able to sleep causes them stress and worry. 86% of participants said they were dissatisfied with their sleep patterns. 77% said that their sleep issue interfered with their daily functioning – with the greatest impact on cognitive function (42%), household chores (38%) and ability to do physical exercise (38%). 62% felt sleep impacted their couple relationship, and 49% felt it impacted their relationship with their child.

The Complex Relationship Between Insomnia and Mental Health
Many people with insomnia also struggle with coexisting mental health issues, amplifying the burden of both conditions. Research suggests that 20–40% of insomnia patients also experience mental illnesses such as anxiety, depression, or bipolar disorder (https://pmc.ncbi.nlm.nih.gov/articles/PMC4187404/). Insomnia is nearly universal among those with depression, occurring in over 90% of cases (https://pmc.ncbi.nlm.nih.gov/articles/PMC5906087/#:~:text=Insomnia%20is%20seen%20in%20more,of%20patients%20with%20clinical%20depression). This link creates a vicious cycle—poor sleep worsens mental health symptoms, while untreated mental illness exacerbates sleep problems.

- Our national sleep and mental health survey showed that individuals with insomnia frequently report feelings of hopelessness, chronic fatigue, and emotional instability. These symptoms reduce their ability to function during the day and limit their capacity to engage meaningfully with work, relationships, and self-care.

The Widespread Impacts of Poor Sleep
Insomnia disrupts nearly every aspect of life, from personal relationships to professional responsibilities. The data collected by MDSC demonstrated that those with the condition often experience exhaustion, cognitive fog, difficulty concentrating, low motivation, and physical ailments like tension headaches or stomach issues. According to the American Psychiatric Association, this can lead to emotional distress, impaired decision-making, and reduced capacity to perform daily tasks. Sleep deprivation also increases the likelihood of accidents, with research indicating it contributes to nearly 40% of reported traffic collisions (American Academy of Sleep Medicine, Morin 2020a).

"Sleep impacted my performance at work, eating habits, cognitive function, energy level/fatigue, partner/relationships and my mood."

"A lifetime of chronic insomnia has led to a lifetime of physical and emotional pain."

"It impacts all areas of my life. Memory function, energy, migraine, inability to be present to events and for my children. Insomnia is devastating."

Another person MDSC spoke to described the emotional toll of managing insomnia as, "Extreme. Effects daily functioning and managing of anxiety and emotions. Quick to anger, and low motivation."

"The most significant is knowing that I need to sleep, but because I cannot shut down the thoughts, I toss and turn…makes for an incredibly long next day, and reduces productivity." And*, "It had a very constant draining effect on my emotional well-being."*

"I've been a bad sleeper all of my life. It was not until I had another medical issue that exacerbated my sleep that I began to try to address my insomnia. It has changed every aspect of my life – I just came to live with being chronically fatigued at work; I went to bed earlier than anyone I knew, but of course, the irony was that I couldn't sleep; when I inevitably woke in the night I would just get up and start working; friends and family holidays and gatherings with an overnight option were a 'no go' because I would need so many accommodations for myself that it wasn't feasible; I only drove if I had to."

- The results of MDSC national survey on sleep and mental health showed that 34% of survey respondents missed time at work, school, or volunteering; on average these respondents missed eight days. Those with a mental illness diagnosis reported 11 days of missed work. All of the individuals MDSC spoke with one-on-one reported that they missed days of work, and while at work they reported not functioning at full capacity because of insomnia.
- Migraine Canada's survey asked respondents to what extent sleep problems interfere with daily functioning (i.e., daytime fatigue, ability to function at work/daily chores, concentration, memory, mood) - over 40% had much or very much interference. Only 20% reported a little impact. The greatest impact was on energy levels. It had a weighted average of 3.1. This indicates that a significant portion of respondents (43.18%) regularly or always felt their energy levels were affected. Cognitive function (focus, attention, and memory) was also regularly affected for over 34% of the respondents who reported regular or constant difficulty in this area.
- Additional areas reported in Migraine Canada's survey that are impacted include performance at work, partner relationships/intimacy, and social interactions. They had weighted averages of 2.3, 2.33, and 2.47 respectively. They also showed negative effects to a slightly lesser extent of 20.80%, 27.91%, and 33.59%, respectively.

One person MDSC spoke to told us that she went off work for two years to try to get her chronic insomnia under control. This work absence meant that their family was living off one less salary during that time, which in turn added more stress to the household:

"As teachers, we are able to distribute our salary over a longer period of time and take time off. For example, I could get paid for 4 years of work, over a 5 year span of time. This allowed me to take a year off within those 5 years. I took that year off twice in 10 years in order to try to get a handle on my insomnia. The only thing I did in those off years was try to sleep during the day when everyone else was out of the house."

Another person MDSC spoke to said she would be present at work, but was not functioning at her full capacity because of her insomnia.

Ripple Effects on Families and Caregivers
Insomnia doesn't just affect individuals—it ripples outward to impact families and caregivers. The data MDSC gathered showed that partners and family members often endured sleepless nights alongside their loved ones, leading to stress, frustration, and relationship strain. Parents said their ability to care for children was diminished, while spouses reported often taking on additional household responsibilities. The data showed that social connections were also weakened as people with insomnia withdraw due to fatigue or unpredictable energy levels, further isolating them and creating emotional distance between friends and family members.

"We talk about sleep for our daughter that we care for every single day."

And about the impact on the parents themselves, "We [mother and father] worry about it [daughter's insomnia] every singe day, because if our daughter has poor sleep, it impacts our daughter's health overall because of her weakened immune system; and if the daughter's health overall fails, then she'd have to go to hospital."

A Need for Access to First-Line Treatment - CBTi
Cognitive Behavioural Therapy for Insomnia (CBTi) is the recommended first-line treatment for chronic insomnia. It targets the thoughts, behaviours, and emotions that perpetuate sleep difficulties. CBTi is backed by strong evidence and is widely regarded as a safe, sustainable, and effective approach to improving sleep quality and reducing relapse. Any treatment plan should begin with or run concurrently with CBTi. However, despite its benefits, our data showed that people face barriers to accessing CBTi. These include stigma around seeking help, lack of public coverage, and practical challenges such as scheduling or attending sessions. Further, not at physicians prescribe CBTi or are knowledgeable about it. CBTi may also be less suitable for individuals with complex mental health needs or learning difficulties, and it can be emotionally demanding, particularly in the early stages as it involves confronting one's emotions and anxiety. As such, while CBTi should remain the foundation of treatment, it is critical that patients also have access to safe and effective medical options when needed.

An Urgent Need for Better/Safer Medical Treatments
From a medication perspective, the risks associated with current/older sleeping pills are well-documented and deeply concerning. These medications can cause memory problems and have been linked to increased rates of dementia later in life. They impair balance and reaction time, making falls a major risk—particularly for older adults, often resulting in fractures, head injuries, or even death. Sleep medications also compromise safety on the roads: people who take them are significantly more likely to be involved in serious traffic accidents, with some studies showing impairment comparable to being over the legal alcohol limit. Dependence can develop in as little as two weeks, with withdrawal symptoms and rebound insomnia commonly reported. Sleeping pills are also associated with increased risk of pneumonia, dangerous drug interactions, and overdose—especially when combined with opioids. Even the next day, people may experience a "hangover effect," with sluggishness and mental fog that interferes with daily functioning. These harms highlight the urgent need for insomnia treatments that are not only effective but also safe and sustainable for long-term use.

From the data MDSC collected and people we engaged, many of these issues were validated with people reporting the following: fear of dependency from past experiences, cognition/memory problems, unsteadiness of movement including fear of driving, and next-day sluggishness/fog. A number of data demonstrate a lack of dependency risk for Dayvigo, as well as the DORA class in general. This data is supported by feedback received by individuals MDSC spoke to who noted they didn't fear dependency with Dayvigo per conversations with their health-care providers.

Other quotes from people MDSC interviewed that help to demonstrate the impact of chronic insomnia:

"I was a young person, just building my career, yet I was so sleep deprived that I really just functioned to get through the day as best as I could. If I didn't have insomnia, I would have had a more fulsome career. I would have been able to do more."

"I honestly don't know how I functioned on 1-3 hours of sleep a night. I really just had to rally and get through the day. It was just one step in front of the other. It wasn't living. I could barely think."

"Because I was so exhausted all the time, I only focused on doing what was essential. Because I had a small child, I had to be a mother as best I could. But outside that, I had to stop everything else – I couldn't do any fitness, I barely saw my friends, I'm not sure how my husband managed to stay married to me."

And some quotes from Migraine Canada's survey:

"When I was in my 20s and 30s I felt ill, couldn't focus, couldn't motivate myself etc. when I had a bad sleep. Late for work. Left early, took extended lunch to sleep etc. As I've aged, I've managed to just get on with life, even when I haven't slept well. It's just a super frustrating way to live. I know I'm short tempered and grumpy when I haven't slept. And, if I have something important the next day the stress of not sleeping is high."

"1. I cannot function on days with only 3-4 hours of sleep which happens so often. I'm unable to make plans because I don't know how I will sleep. 2. I often dread going to sleep or trying to get back to sleep because it seems so difficult & unsuccessful. I have a lot of anxiety about sleeping because of this. 3. I also struggle because everything I use to improve my sleep gives me a hangover, whether or not it works."
"It impacts all areas of my life. Memory function, energy, migraine, inability to be present to events and for my children. Insomnia is devastating."

"With insomnia, it is challenging to feel happy and energized. I have struggled to get up in the morning, feel motivated to work or engage with other people. I feared going to bed each night because often times I would just lie there, frustrated and exhausted."

"In the past year, my stress/worry level about my sleep issues is at 8-10, with 10 being extremely worried. The emotional toll of managing insomnia for me is extreme. [It] effects daily functioning and managing of anxiety and emotions – [I'm] quick to anger, and [have] low motivation."

4. Experiences With Currently Available Treatments (other than the drug under review)

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

The following section also draws from previous CDA-AMC and INESSS submissions and remains largely unchanged. However, for this submission, MDSC conducted additional conversations with patients who have experience using current insomnia treatments—excluding the drug under review. These discussions reaffirmed the original findings: patients remain overwhelmingly dissatisfied with existing therapies; many reported dissatisfaction due to intolerable side effects, particularly next-day sedation, cognitive impairment, and a persistent fear of developing dependency. These additional accounts have helped to enrich and validate the narratives captured below, reinforcing the urgent need for safer, more effective treatment options for chronic insomnia.

Pathways to Treatment – Step One

Insights gathered from patient experiences highlight a typical progression in how people seek relief from chronic insomnia. Initial efforts often involve self-management through over-the-counter (OTC) remedies and self-medication. Common choices include antihistamines (e.g., Benadryl, Nytol), melatonin, magnesium, or analgesics like Advil or Tylenol, along with natural supplements. Many patients also attempt lifestyle adjustments such as improving sleep hygiene, reducing caffeine and screen time, adopting relaxation techniques, or making dietary and exercise changes. However, when these approaches fail to bring relief, some individuals may resort to risky methods, such as alcohol or recreational drug use.

One patient MDSC interview noted, "I also took large amounts of Benadryl and melatonin for years before stopping a couple of years ago, once I realized the cognitive effects/risks. I also take Seroquel and have done so for 2 years. [Although] I have had to increase to higher doses of Seroquel, and will likely need to continue increasing [the doses] to support my sleep needs."

Patients typically seek medical advice only when the condition starts to severely impact their ability to meet daily responsibilities. By then, the chronic nature of the condition often makes it harder to manage, as the persistent cycle of poor sleep has already deeply affected their quality of life.

Limitations of Current Prescription Treatments – Unmet Clinical Needs

Research from MDSC has revealed that currently available prescription treatments for insomnia, while sometimes effective in the short term, are frequently associated with significant drawbacks. Patients reported that medications like benzodiazepines and non-benzodiazepine hypnotics (Z-drugs) helped some individuals fall asleep but were are far from ideal. Patients reported side effects such as next-day drowsiness, cognitive impairment, weight gain, rebound insomnia, and dependency. Over time, patients often developed a tolerance to these medications, making it difficult to stop taking them—even when the treatment was no longer effective or satisfying. People with mental illness are particularly vulnerable to addiction with benzos. Many described the process of discontinuing these medications as more distressing than the insomnia itself, further entrenching the cycle of dependency.

One person MDSC spoke with said the following with respect to any concerns around long-term use of Rx medications previous to Dayvigo: "My biggest concern is related to the tolerance I might create when using regularly, and the cost associated with increase use of it [Seroquel]."

Another person said of limitations of previous treatments: "Withdrawal from Klonabin was very disruptive and dangerous."

And another individual with respect to trying a new medication noted, "If a new medication would become available, I would be willing to try it, as long as it was not in a class where prolonged use could be harmful."

- In Migraine Canada's survey, respondents reported using the following prescription medications: benzos (17%), flurazepam (2%), temazepam (2%), zopiclone (Imovane) (27%), zolpidem (Sublinxo) (8%), exzopiclone (Lunesta) (2%), triazolam (1%), DORA (1%), lemborexant (Dayvigo) (9%), daridorexant (Quviviq) (1%), trazadone (27%) quetiapine (12%), mirtazapine (5%), gabapentin (24%), pregabalin (6%), other: unknown name, Avantil for migraines, clonzaempam + amitriptyline, Xyrem, cyclobenzaprine, others, prazosin, clonidine, sertraline, anxiety meds, Concerta, propranolol, tryptophan, Stamoc, lorzaepam, prazosin (29%)

One person MDSC interview shared that she, "Had been prescribed other various medications like mirtazapine, and then antidepressants (in the context they would help to support sleep but also reduce anxiety). [I tried] trazadone - disrupted my sleep, and caused dizziness the next day, doxepin; Silenor for insomnia – tried for 2 days and then stopped due to unsafe thoughts; mirtazapine - took for a few weeks and then stopped as it caused weight gain, poor motility, and didn't improve sleep and I had trouble with memory; amitriptyline – tried it for 3 weeks and stopped due to painful bloat/constipation and didn't improve sleep, created low mood. None helped. [They] didn't help with insomnia and caused fatigue, nightmares, bloating and constipation, and [made me] groggy,"

"1. I cannot function on days with only 3-4 hours of sleep which happens so often. I'm unable to make plans because I don't know how I will sleep. 2. I often dread going to sleep or trying to get back to sleep because it seems so difficult & unsuccessful. I have a lot of anxiety about sleeping because of this. 3. I also struggle because everything I use to improve my sleep gives me a hangover, whether or not it works. 4. Even worse than the above is the inconsistency I find with medications & supplements. They seem to work about 50% of the time, & I'm unable to predict whether they will or won't work."

One patient noted they experienced the following while taking prescription medications prior to Dayvigo: cognition issues, weight gain, groggy/sleepy, fatigue, nightmares, bloating and constipation.

One patient MDSC spoke to stated the following about other treatments she tried: "I also take Seroquel, and have done so for 2 years. Had been prescribed other various medications like mirtazapine, and then antidepressants (in the context they would help to support sleep but also reduce anxiety). None helped. I also took large amounts of Benadryl and melatonin for years before stopping a couple of years ago, once I realized the cognitive effects/risk."

"I was prescribed sleeping pills at one point, but they were too strong and made me groggy. I haven't discussed it [again] until recently."

"Everyone tried to give me pills but everything I've taken has side effects I can't live with, ranging from weight gain to 'hangover' effects."

One person described taking prescription, "Medication that made me feel awful".

When asked specifically about any antidepressants tried previous to Dayvigo:

> *"trazadone (Desyrel, Oleptro), disrupted my sleep, and caused dizziness the next day, doxepin (Silenor) for insomnia, tried for 2 days and then stopped due to unsafe thoughts; Sinequan (for depression/anxiety), quetiapine (Seroquel) currently take, mirtazapine (Remeron) took for a few weeks and then stopped as it caused weight gain, poor motility, and didn't improve sleep and I had trouble with memory, gabapentin (Neurontin), pregabalin (Lyrica), amitriptyline (Elavil) – tried it for 3 weeks and stopped due to painful bloat/constipation and didn't improve sleep, created low mood, olanzapine (Zyprexa)."*

Patients also noted that these treatments generally address only one aspect of insomnia, such as initiating sleep, without providing a holistic solution that ensures restorative and uninterrupted rest. A particularly troublesome side effect patients reported is the sedative hangover many experience, leaving them feeling groggy, sluggish, and unproductive the following day.

Exploration of Non-Medicinal Therapies, including CBTi
In their pursuit of relief, many patients reported turning to a range of non-prescription interventions, including mindfulness exercises, relaxation techniques, CBTi, and rehabilitation programs.

While some patients reported finding these approaches beneficial, they also noted they faced accessibility challenges, with public psychological support difficult to obtain without significant out-of-pocket expenses. Some others reported these methods were only partially effective or failed to provide sustained relief. Even procedures like sleep studies, while helpful for diagnosing issues, rarely led to immediate solutions and involved long waiting periods.

In MDSC's survey:

- One-half of respondents (50%) reported using physical exercise to help them sleep.
- One-third (31%) used OTC medications to help them sleep.
- Of respondents who have been formally diagnosed with a sleep disorders, 9% have tried bright light therapy, 7% have tried CBT, 10% use a breathing machine for sleep, and 20% have tried a wearable device (Fitbit, Apple watch, Oura ring, etc.).

Regarding CBTi, one patient in Migraine Canada's survey noted, "I do think the CBTi helped, but it wasn't as accessible as I needed".

Two of the individuals MDSC interviewed said the following about their CBT experiences: "I tried CBT a few times but didn't find it really helped. Since it wasn't really that useful to me, and I would have had to pay for it myself, which I can't afford, I stopped trying it."

"I did find that CBT helped me. I only learned about CBT when I was trying to manage how many pills I was taking to manage my insomnia. I wish I knew about it from the start. I continued to see my therapist for more than 20 years, but she's now retired and so I stopped going. What I learned in CBT still helps, but it's not perfect. I still have many episodes of insomnia. Of course all of it was paid for by ourselves – the first few sessions were covered by my workplace plan each year, but after that we were on our own."

Harmful Coping Strategies

In their desperation to achieve better sleep, some patients reported experimenting with harmful practices, including combining OTC medications with alcohol, straight alcohol or cannabis. Patients noted that while such approaches initially appeared to alleviate symptoms, they didn't solve the problem, and in some cases, seemed to make it worse. Certainly, it is shown that while alcohol may initially help people fall asleep, it disrupts the sleep cycle, leading to frequent awakenings, poor sleep quality, and diminished REM sleep. Similarly, chronic cannabis use has been proven to result in tolerance, dependency, and withdrawal symptoms, further complicating sleep and overall health. Of course, these behaviors not only fail to resolve the underlying insomnia, but may also lead to addiction, worsen co-occurring mental health conditions, and place additional burdens on healthcare and social systems.

One person we spoke to noted they would take an OTC medication and alcohol together as she had read on the internet that this may be effective for insomnia without being addictive, and it did provide her with some relief initially.

One individual MDSC spoke to said, "I have been sober for 2 years, but [alcohol] didn't improve [my] insomnia."

- In Migraine Canada's survey, 6% of respondents reported using alcohol and 27% reported using cannabis as an OTC remedy to improve their sleep and insomnia.

Inappropriate Use of Current Medications

The improper use of existing prescription medications remains a pressing concern. Many of the drugs currently prescribed for insomnia, such as benzodiazepines and Z-drugs, are not recommended for long-term use. Prolonged reliance on these medications can lead to harm, particularly given their dependency risks and withdrawal challenges. This was an underlying concern presented by much of the data that MDSC collected.

There are ongoing efforts in Canada to address the inappropriate use of medications, highlighting the need for treatments better suited for chronic insomnia. The healthcare system bears significant costs, both in addressing the consequences of prolonged use of outdated therapies and in supporting patients as they attempt to transition off these drugs.

Additional quotes from individuals MDSC interviewed and Migraine Canada's survey that describe the impact on the insomnia medications they tried:

One patient described, "I had to keep taking higher doses of my insomnia medications in order to get the same effect. This was insidious. But at a particularly low point, I called my best friend over and together with my husband we tried to plot out what I could possibly do to get a handle on my sleep as it was clear that what I was doing wasn't going to be sustainable. Eventually, there would not be enough pills to keep me sleeping."

And other person: "My biggest concern is related to the tolerance I might create when using regularly…"

5. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

Again, the following section is drawn from previous CDA-AMC and INESSS submissions and remains largely consistent with earlier findings. However, MDSC engaged additional patients with experience using current insomnia treatments—including and excluding the drug under review—to further inform and validate the content around what improved outcomes patients desire. These new conversations confirmed that while many patients ideally wish to avoid medications altogether, they recognize that drug therapy is sometimes necessary. In those cases, they strongly emphasized a preference for treatments with minimal side effects, particularly reduced risk of dependency. Patients consistently expressed a willingness to tolerate some side effects if it meant achieving one crucial outcome: the ability to function during the day with alertness and clarity. This updated input has been integrated throughout the section below to reflect the lived priorities of those managing chronic insomnia.

Minimizing Side Effects for Sustainable Use
Patients with chronic insomnia have emphasized to MDSC the critical importance of minimizing the adverse effects of treatment. Many who had used benzodiazepines or Z-drugs reported challenges such as cognitive issues, daytime grogginess, and the development of tolerance and dependency, which left them reliant on medications longer than intended. Additionally, patients on antidepressants or antipsychotic medications for co-occurring mental illnesses often noted that these treatments did little to address their sleep problems, and in some cases, exacerbated them. Patients told us that the ideal medication for insomnia should allow for temporary use without creating severe withdrawal symptoms, enabling patients to discontinue safely once their condition improves.

- In MDSC's survey, 20% of respondents reported currently taking prescriptions medications for their mental health. Of these, only 54% felt the medication had a positive impact on their sleep, while 83% felt the medication had a positive impact on their mental health.

MDSC also asked people it connected with one-on-one what trade offs they would make to be well treated:

"I would expect some 'hangover' effect in the morning as long as I know the class of drug will not do me harm over an extended period."

"I would foremost want to know it is safe to take say once or twice a week without causing me harm. I would also want to have the medication to take effect 1 hour after I take it, and to stay effective until 5 am the next morning."

"I'd give up driving if it meant I could sleep at night – really sleep at night so that the next day I felt normal enough to go through the day taking care of my kids and going to work…you know, just being a normal, productive member of society."

"Knowing that after taking a sleeping pill, sleep is a sure thing, I'd be happy to navigate some initial grogginess upon waking." And, "If it wasn't effective and it was associated with side effects, then no point to taking it really."

Balancing Efficacy and Quality of Life

From the patient perspective, the most significant improvement sought in insomnia treatment is the ability to function well during the day. While symptom relief at night is essential so patients can sleep, patients consistently voiced the need for better daytime outcomes—feeling rested, alert, and ready to participate fully in their daily lives. Patients reported that current medications often left them feeling groggy or fatigued, compromising their ability to work, think clearly, and engage in their routines. Patients said they want treatments that provide a restorative night's sleep without impairing their cognitive abilities or physical energy the next day. The ultimate goal for many is achieving a sense of normalcy, allowing them to meet professional and personal responsibilities without compromise.

Ensuring Equitable Access

Access to effective insomnia treatments remains a significant concern for patients and caregivers from the data MDSC gathered. Many individuals expressed frustration over inequities in treatment availability across provinces and territories and emphasized the need for affordability. Whether through public healthcare systems, private insurance, or manufacturer assistance programs, patients believe all Canadians should have equal access to medications that improve their sleep and overall health.

Patients stressed to MDSC the importance of having informed, accessible choices in managing their insomnia. Recognizing that individual responses to treatment vary based on genetic, physiological, and environmental factors, they highlighted the need for flexible treatment options. This empowers patients to work collaboratively with healthcare providers to select medications that align with their personal needs and preferences, fostering better adherence and outcomes.

It is important to note that with respect to access, patients with mental illnesses are often in precarious financial situations, exacerbated by unemployment or underemployment. Statistics reveal that over half of Canadians with mental health-related disabilities are unemployed, with the figure rising to 70–90% for those with severe mental illnesses. Additionally, in the survey Migraine Canada conducted, close to 17% of respondents were on disability. This reality underscores the necessity of including all treatments in public drug plans to ensure no one is left without support due to financial constraints.

Hope for a Novel Treatment Approach

The prospect of a new medication that operates through a novel mechanism of action ignited a sense of hope among patients and caregivers MDSC engaged with. The individuals MDSC interviewed expressed optimism that such a treatment could address insomnia without the debilitating side effects associated with other medications they've tried. They hoped that this innovative option would not only improve sleep initiation and maintenance but also allow them to enjoy the benefits of restorative sleep without dependency or residual sedation.

A person MDSC connected with one-on-one said regarding hope for a new medication: "My first medication seemed to work at the start, as at this time in my life, I had not slept for 3+ months hardly at all, so when I took the first medication, it allowed me to fall asleep and stay asleep all night (I was exhausted). It worked OK for the first month, then I started to notice many bad dreams as well as I would feel tired and sluggish in the mornings; it seemed like it was still impacting my system the next day. If I could change something about the first med, it would be to eliminate these two side effects." And*, "It did help me sleep, it was the side effects that I did not like."*

One patient MDSC interviewed said that compared to their ability to sleep before (1-2 hours a night), the prescription medications she had tried in the past did help her to fall asleep, but then she would wake 3-4 hours later, not feeling fully rested. This patient noted that while it wasn't a "full night's sleep" or "fully restorative sleep", it was better than 1-2 hours of sleep so she accepted it. The idea that there could be something even better out there that would help with both falling asleep and staying asleep, thus, having better total overall sleep, was considered "something magical I would do anything to get".

Regarding what improvement she could see with a new medication with a novel MOA and not the side effects she had before: "It would be life changing."

Some additional verbatims from Migraine Canada's survey sharing what success with a new medication would look like:

"Waking up feeling rested."

"Sleeping through the night with no hangover and no weight gain at least 5 nights a week."

"Be less tired all the time. Have more energy. I probably would hurt less and be a more productive human being with a positive attitude."

"Occasional sleep issues would be success, but of course having no sleep issues would be optimal. That's hard to imagine though. It would be so uplifting to wake up fully rested and ready to tackle the day instead of triggering a migraine and struggling through the day."

"Decreased anxiety and depression, less irritability, more energy, desire and ability to go out more, exercise tolerance, ability to socialize more, ability to do more than the absolute minimum of housework and shopping."

"Freedom to live my life, make plans, less stress & anxiety. It would give me many more hours a day of life, instead of wasting time in bed, unable to sleep or unable to wake up from the hangover caused by meds/supplements."

"Success would be falling asleep with ease, and having quality sleep for the 8-9 hrs a night I need, waking up feeling rested and having the energy and capacity to fully show up in my life."

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways? If applicable, please provide the sequencing of therapies that patients would have used prior to and after in relation to the new drug under review. Please also include a summary statement of the key values that are important to patients and caregivers with respect to the drug under review.

For this section regarding direct experience with Dayvigo, MDSC connected with 6 individuals in total. In addition, the Migraine Canada survey included 14 people with experience on Dayvigo.

Of the six individuals who MDSC connected with one-on-one, four accessed Dayvigo via private workplace insurance, with one person paying out of pocket for it (as it was not covered by her workplace insurance plan), and one person said that while they did have private coverage it was not full coverage and they relied on provincial coverage for prescription reimbursement, including for Dayvigo. Ages ranged from 41-50, 51-60 and 61+. Of the four individuals who had Dayvigo covered via private insurance, one person noted they had an additional monthly co-pay:

"I do have to pay ~$20 extra each month for my prescription renewal compared to my previous medication, but it's worth it."

The six individuals listed the medications they had tried prior to Dayvigo (some individuals had tried multiple medications in the past):

- 2 had tried melatonin in the past
- 2 had, on occasion, used Gravol,
- 4 had used zopiclone
- 3 had used quetiapine/Seroquel; one had used Seroquel (100mg) and they stated that the dose left them feeling very tired the next day
- 1 had tried clonazepam/Klonopin
- 1 had tried diazepam/Valium
- 1 had tried trazdedone
- 1 had tried doxepin
- 1 had tried mirtazapine
- 1 had tried amitriptyline

Benefits of Dayvigo

The key feedback provided by individuals MDSC connected with regarding the benefits of Dayvigo were around the areas of improved side effect profile and improved efficacy. From an efficacy standpoint,

patients MDSC spoke with expressed that Dayvigo improved both their sleep initiation and maintenance, ensuring that they fell asleep faster and also stayed asleep longer. Patients reported having more restorative sleep and a better quality of life.

Specifically, with respect to efficacy, one person noted Dayvigo allowed them to go to sleep quickly – within 20 minutes, and that it improved how long they slept in a night (allowing for at least 6-7 hours/night of sleep). They noticed the improvements "right away" after starting Dayvigo.

Another person also noted Dayvigo helped them get to sleep quicker – improved by, on average, one hour. This person added that it also improved how long they slept in a night: *"When I take it, I will sleep until about 5:00 am. I will wake up once at about 1:00 am to use the bathroom, but am able to go back to sleep…which is very good."* They added that it helped the total time they were able to sleep each night by 1-1.5 hours, and they experienced all these improvements within the first 2-3 nights after starting Dayvigo.

One individual noted that on Dayvigo, "I have more energy during the day, because I sleep through the night". Another said, "It has helped. I feel more rested, and I am able to feel more relaxed."

Two individuals identified they no longer felt anxious or stressed on Dayvigo, because they no longer worried if they were/weren't going to sleep. Stress levels regarding sleep issues previous to taking Dayvigo (where 10 is extremely worried and 1 is not very worried) were nine for one individual, 8-10 for another individual, while a third individual noted they were at a 3 previously.

Side Effects of Dayvigo

Specially regarding an improved side effect profile, one person noted they experience some dryness of mouth, and, on occasion, had dreams, but, *"not as weird as [dreams while taking] previous [medications]."* Another person noted they felt the need to take some deep breaths after taking Dayvigo and getting into bed. And a third person noted the side effects were minimal and required no management.

MDSC asked three people how much improvement Dayvigo provided compared to previous treatments with the following responses: *"Excellent", "Much gentler, and I feel more able to take it without worrying it is causing me harm", "Better".*

Some additional verbatims from patients MDSC interviewed regarding their experience with Dayvigo:

One patient stated that he, "felt the impact of using Dayvigo immediately. It worked without delay and felt that all of a sudden, he had a new treatment to take that addressed his insomnia problems that have been having a direct negative impact on his working days for far too long. Along with providing a new option, it offered him relief and hope."

One patient was impressed at how quickly Dayvigo worked, stating that he was able to improve his sleep after only one day, and this was not his experience with other insomnia medications he's tried in the past. This patient described the impact of Dayvigo to be clinically significant, compared to other medications he has tried, in that it worked quickly to provide him with uninterrupted and restorative sleep, and worked quickly to keep him alert during the day, without the fear of dependency. This patient had reviewed the clinical data, which demonstrated a lack of dependency for Dayvigo - this lack of dependency provided the patient with less stress

and anxiety knowing that when he went off the medication, he wouldn't have to suffer the negative impacts and experience from having try to go off previous medications. During the daytime, this patient described feeling like his old self – he felt productive at work, and was able to maintain healthier relationships with coworkers as he described not feeling groggy or grumpy. He described having minimal morning residual effects.

Another patient on Dayvigo explained that the medication not only initially worked quickly to get her to sleep, but also stopped quickly so that she didn't feel groggy and sedated the next day.

Another patient we spoke with noted that it was after many months of suffering with little more than two hours of sleep per night, he finally went to see his physician. The first medication that the physician prescribed did not work well for the patient as it resulted in severe nightmares every night. "The nightmares were bizarre and unsettling." The second medication (Dayvigo) his physician prescribed provided immediate relief for this patient – the patient described previously feeling like he was, "an old, broken-down car with flat wheels that were covered in so much mud that the car was too heavy to move forward – to being able to see through the windshield, feeling like all the mud was washed away and he could drive again."

"I am finding I am seeing the ability to be able to level off my irregular sleeping patterns, and trust that I will be able to feel rested when I go to work the next day" And, "[My stress is reduced by] not having to only rely on waiting until near midnight each night before I finally drift off to sleep, only to waken by 3."

One person expressed feelings of not wanting to become dependent on the medication over the long term. They have been looking for a medication that was gentle on their stomach and not overpowering, which they claimed to feel with this medication. They stated while it, "was too soon to see any pronounced impact, they did not have the feeling of next morning dullness and drowsiness," which they have had in the past.

This patient stated she had tried several different medications in the past, and all seemed to lose their effectiveness after several weeks, leading to having to increase the dosage, which resulted in her feeling hung over the next day. She expressed she has tried Dayvigo, which was working for her without any major side effects. With Dayvigo now she was spending, "Less time laying there tossing and turning now".

And from the Migraine Canada survey:

"Dayvigo is the best thing that has happened to me. No groggy/brain fog side effects. Been on it for two years now."

"Dayvigo has helped my sleep immensely."
"Discussed [with physician] and tried Dayvigo, this has brought significant improvement."

For an audio clip of a patient describing his experience on Dayvigo, please follow the link below:

https://drive.google.com/drive/folders/11wtTXrvGrtNXL0iRHGpr4KtP3WAPY7ga?usp=sharing

Through one-on-one conversations, interviews, and survey data, MDSC consistently heard from patients who had taken Dayvigo that the improvements they experienced were significant — often far exceeding the benefits of previous treatments. What stood out even more was that these gains came with fewer side

effects and, importantly, without the fear of dependency that had accompanied other medications – and that the benefits began fairly quickly after starting Dayvigo.

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

<Enter Response Here>

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

In its original 2022 assessment, (then) CADTH noted that the clinical trials for Dayvigo excluded individuals with conditions such as sleep apnea, anxiety, and depression—leading to uncertainty about the treatment's effectiveness in these populations. However, through MDSC's data and outreach for this submission and Migraine Canada's survey, patients with these very conditions were represented and shared valuable real-world insights. MDSC's feedback includes individuals managing insomnia alongside anxiety, depression, and sleep apnea—underscoring that these comorbidities are common and relevant to real-world treatment contexts. Further, in Migraine Canada's 142 survey respondents, 27% reported having tried zopiclone (Imovane), and 8% had experience with zolpidem (Sublinxo), despite zolpidem not being indicated in Canada. One individual with a history of shift work and co-occurring mental health issues described to MDSC having trying zopiclone in 2005, recalling a "metal taste" and no meaningful improvement in sleep. Three other people MDSC spoke with one-on-one had tried zopliclone previous to Dayvigo. These findings suggest that Canadians do have experience with the drug class used in the comparator arm of the trial. When considering reimbursement, it is essential to balance trial data with lived experience.

Heterogeneity and Mental Illness

Given the heterogeneity of mental illnesses and the diverse ways individuals experience and respond to treatment, it is essential to have a range of therapeutic options for managing chronic insomnia—particularly those that move away from older, medications like benzodiazepines and Z-drugs. These drugs carry well-documented risks of dependency, cognitive impairment, and other harms, which are especially concerning in an already vulnerable population, such as those with mental illnesses. Additionally, the mental illness

community often faces unique challenges when it comes to participating in clinical trials, making evidence generation more difficult. As a result, decision-makers should allow for a greater degree of uncertainty in the clinical data when evaluating new treatments for mental illnesses, recognizing the ethical and practical barriers to conducting large, traditional studies in this population. A more flexible, compassionate approach to evidence assessment is critical to ensuring access to safer, more appropriate treatment options for those who need them most.

Addressing Inequities in Access to Care
An issue in insomnia, and all mental illness, treatment is the disparity in access to effective care, particularly for those in lower socioeconomic groups or in underserved regions. Many individuals face significant barriers due to the high costs of treatment or lack of public funding for therapies like CBT-i, perpetuating health inequities. Ethical considerations demand a focus on making effective treatments widely available and affordable. Without equitable access, individuals unable to afford care are left to struggle with untreated insomnia, exacerbating their health issues and quality of life.

The Societal and Economic Impact of Insomnia
As noted earlier in this submission, the ripple effects of untreated chronic insomnia extend far beyond the individual. On a societal level, sleep deprivation contributes to increased healthcare utilization, workplace absenteeism, and diminished productivity. Insufficient sleep has been linked to traffic accidents, workplace errors, and a substantial economic burden. The estimated economic cost of insomnia symptoms in Canada is $1.9 billion annually. This figure includes direct costs like healthcare expenses and indirect costs like reduced productivity and absenteeism. Additionally, individual economic burdens of insomnia are estimated at $5,010 per person per year, with nearly 90% attributed to indirect costs (https://www150.statcan.gc.ca/n1/pub/82-003-x/2018012/article/00002-eng.htm, https://ottawacitizen.com/news/local-news/the-high-cost-of-poor-sleep-from-physical-and-mental-illnesses-to-economic-hits#:~:text=Too%20little%2C%20low%2Dquality%20sleep,billion%2C%20according%20to%20Canadian%20research). The burden of insomnia also affects societal participation, as individuals often withdraw from social activities and community engagement due to fatigue and poor health. These challenges highlight the far-reaching implications of chronic insomnia, emphasizing the urgency of addressing its treatment.

The Complex Nature of Insomnia and Comorbidities
Insomnia is often intertwined with other health conditions, such as anxiety, depression, and cardiovascular disease. These comorbidities create a complex treatment landscape, as the presence of one condition often exacerbates the other. For many patients, the stigma surrounding insomnia further complicates their willingness to seek treatment.

Stigma
While public awareness around mental health has improved, stigma remains a significant barrier that prevents many people from seeking the treatment they need. On top of that, an added layer of stigma surrounds prescription medications — driven by the misconception, even among those who are struggling, that mental illness, including insomnia, isn't "serious enough" to warrant medical treatment, despite the fact that for many, these medications are essential and life-changing.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

This submission was written by a consultant that works primarily with Mood Disorders Society of Canada free from consultation, advice, influence or financial support from any outside individual, group, or company.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

MDSC worked with Narrative Research on its mental health and sleep survey. Migraine Canada shared it's sleep and migraine survey with MDSC.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
J&J				x
Pfizer			x	
Lundbeck-Otsuka Alliance				x
AbbVie Inc.				x
Eisai				x
Idorsia			x	
Boehringer-Ingelheim				x
Biogen			x	
Takeda			x	
Teva			x	
IMC			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.

Name: Dave Gallson
Position: National Executive Director
Patient Group: Mood Disorders Society of Canada
Date: April 24, 2025

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

Reimbursement Review

Clinician Group Input

Project Number: **SR0895-000**
Generic Drug Name (Brand Name): **Lemborexant (Dayvigo)**
Indication: **Chronic insomnia**
Name of Clinician Group: Addiction Medicine Specialists
Author of Submission: Drs. Shaohua Lu, Sam Chang, Timothy Moran, Risk Kronfli, Nancy Légaré, Tin Ngo-Minh, Ravinder Mankoo, Marie Hélène Geoffroy

1. About Your Clinician Group

We are a group of psychiatrists and a psychiatric pharmacist representing specialists who treat patients with addictions. Some of us also treat patients in a specialized environment like correction health and forensic settings with a high percentage of co-morbid addiction issues.

2. Information Gathering

We convened for the purpose of preparing input for Canada's Drug Agency (CDA) based on the negative impacts we see on our patients related to the need to prescribe ineffective and, in some cases, harmful medications for sleep. We also wanted to discuss our own practice as it relates to substance use, diversion, abuse and some of the data emerging regarding switching from less harmful medications. In addition, addressing long-term reduction in hypnotic use in general.

3. Current Treatments and Treatment Goals

The Canadian Consensus Guidelines for the management of insomnia (December 2024)[1] state:

- Chronic insomnia should be specifically targeted for treatment, even in the presence of comorbidities.
- Cognitive-behavioural therapy for insomnia (CBT-I) is the first-line treatment. Sleep hygiene alone is not CBT-I.
- Benzodiazepines and z-drugs are effective for short-term management, despite concerns about adverse effects and tolerance. Some evidence demonstrated a relative lack of tolerance of eszopiclone.
- Dual orexin antagonists (DORA) may have benefits that outweigh their risks for long-term use (e.g., no tolerance in 12-month studies and absence of rebound in controlled clinical trial).
- There is lack of evidence on the use of melatonin for insomnia treatment; on the long-term effect of cannabinoids; and the benefits of off-label medications (e.g., antidepressants and antipsychotics), in addition to the concerns about their safety profiles.

Cognitive behavioural therapy for insomnia (CBTi) is not widely available or funded in Canada.

For patients that don't respond or can't access CBTi, there are no publicly reimbursed pharmaceutical treatments that address the underlying pathology of insomnia. The available options merely sedate patients helping them get to sleep in the short-term and this is analogous to using a bandage when stitches are required for a longer term cure. In addition, the available options are associated

with significant side effects and risks including dependence, next day sedation and functional impairment, parasomnias, habituation, interactions, cardiac arrhythmias, weight gain, diabetes, dyslipidemia, tardive dyskinesia, etc. and should not be used long term. Therefore, not only are the available treatments not beneficial for sleep architecture, they might also be harming patients when used long term.

There is a clear "continued use" of "sedating agents" in the treatment of insomnia in Canada that is not based on any science. This leads to longer abuse of sedating agents without any "end in sight" for management of insomnia. Moreover, the sedating agents are reimbursed by provinces across Canada for as long as they are prescribed despite the recommendation that they are for short-term use only.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

With respect to individuals with addictions specifically, there is a lack of options for people with co-occuring substance use disorders and sleep issues. There are a multitude of issues with providing sub-optimal treatment for these patients. Not only are the treatments ineffective or harmful for patients with substance use disorders, but there is also a cost to the healthcare system associated with each trial of an ineffective or harmful treatment.

Benzodiazepines or Z-drugs are not options for patients with substance use disorder due to their potential for overuse, misuse or diversion. Benzodiazepines can cause respiratory depression and should only be used short term, after which time they lose efficacy. Quetiapine (Seroquel), although not indicated for insomnia, is often used short or long term and does not improve sleep architecture. In addition, there is a risk of using quetiapine in combination with methadone due to arrythmia risk. Also, some individuals who use stimulants (i.e., cocaine, amphetamine), will often manage withdrawal with "quills" (quetiapine or alprazolam). Trazodone can be offered to these patients due to the lack of abuse potential but taking too much of it can lead to harm especially negative cardiac effects if used in combination with stimulants. Melatonin is not effective for insomnia; it's for individuals with circadian rhythm disorders.

Other important considerations for patients with substance use disorders are as follows:

- Some patients with addictions do not always engage well with doctors. If they engage to get medication, then it must work to build/maintain credibility; if you prescribe something that doesn't work, they will find something that does work and, in this case, it may be cannabis or a street drug.
- Up to 25% of individuals aged 15 or greater report heavy drinking[2] and 6% report consuming cannabis daily or almost daily.[3] When these groups use benzodiazepines, there is an increased risk of motor vehicle and other accidents. If patients are on benzodiazepines or Z-drugs, their risk gets amplified if they are addicted to alcohol. Alcohol is one of the most commonly used legal substances associated with harm and death. The combination of alcohol and benzodiazepines and Z-drugs is potentially deadly, especially for binge alcohol users. Both Z-drugs and alcohol, by their actions on GABA receptors, can trigger alcohol craving.
- Acute benzodiazepine or Z-drug withdrawal can be a life-threatening condition. Physicians need adequate tools to stabilize patient sleep during acute withdrawal. Anchoring their sleep helps with other issues. For this reason, lemborexant was fast tracked to the stabilization unit on the hospital formulary of the Foothills Medical Centre in Calgary because there are no other tools with which patients can be treated.
- Young people are very resourceful. If they need medication to help with insomnia, they are ordering from the dark web or other risky sources. When they come to see us in trouble medically, we often have no idea what type of benzodiazepine or Z-drug they are actually on, and we don't know how to cross-taper them off. The demographic of 18-24 years old is the peak demographic for substance use. These young people are at the start of their education or career. By using suboptimal treatments to manage their insomnia, we are creating a hot bed of heavy drug use in these future leaders of our society. The harms of benzodiazepines and Z-drugs take many years to manifest and, by the time the harms are known, it may be too late to avoid them.

- Patients with addictions are at risk of death when discontinuing benzodiazepines (e.g., risk of death due to cardiac arrhythmia or seizure). As an analogy, the brakes are taken off the patient's brain and the brain can't regulate the nervous system. If we abruptly take them off benzodiazepines, it is of huge concern. There is also a risk of overuse of benzodiazepines.
- There is a high failure rate in treating addiction when patients have insomnia if we don't have the right insomnia treatment. Patients undergoing alcohol withdrawal typically have secondary insomnia and must also withdraw from benzodiazepines. The only way to safely withdraw is by providing the appropriate and safe alternative. Benzodiazepines cause respiratory depression; quetiapine (Seroquel) causes metabolic and extrapyramidal side effects. Addictions have changed the receptors of individuals suffering from substance use for many years, and physicians have to treat the addiction with the appropriate medication that preserves/restores their sleep architecture.
- The current toxic drug crisis means most illicit substances are not pure and are highly adulterated. There are substantial risks for inadvertent overdoses even in casual, recreational drug users. Thus, the combination of unknown substances with benzodiazepines and Z-drugs constitutes an unacceptable risk even for casual users.

Treating insomnia is not just about getting people to sleep. We can give them many treatments to get them to sleep. The question is whether they can function and whether their long-term risks are reduced. In general, when we treat patients with dependence or addictions with the reimbursed options, we are using medications that are potentially harmful out of necessity for a treatment. Patients need options that are beneficial for sleep architecture without doing harm. At about $70 per month for a 30-day prescription, this is a very small cost to save a life.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Lemborexant is a dual orexin receptor antagonist (DORA). DORAs block the activity of orexin which is a neurotransmitter that promotes wakefulness. Lemborexant is the first approved medication for insomnia that treats the underlying disorder and preserves sleep architecture (i.e., achievement of stage 3 and REM sleep). The available off-label and/or unfunded options (benzodiazepines (e.g., lorazepam, temazepam)), Z-drugs (e.g., zolpidem), antihistamines, melatonin receptor agonists, antidepressants, and antipsychotics, variably act as sedatives making patients drowsy and helping them get to sleep but they do not promote quality sleep allowing patients to function the next day.

Lemborexant should be the first line option for patients with addictions based on the data of efficacy and safety and the fact that it reduces the long-term use of other hypnotics. Lemborexant should also be used in combination to reduce other harmful agents. Data suggests that adding DORAs would lead to discontinuation of other agents and eventual discontinuation of hypnotics in general. Similarly, switching to DORAs seems to also lead to eventual discontinuation of hypnotic therapy in general, thus reducing the burden regarding hypnotics/sedating agents in general. Lemborexant should not be reserved for patients who are intolerant to other treatments or in whom other treatments are contraindicated because that would defeat the purpose of achieving wellness and safety.

OAT (opioid agonist therapy) is being widely adopted against toxic opioid drug deaths. Concurrent OAT and benzodiazepines and Z-drugs are considered contraindicated. The Canadian Agency for Drugs and Technologies in Health (CADTH, now Canada's Drug Agency (CDA)) published an environmental scan in 2018 entitled: "Policies to Prevent Harms from the Co-Prescribing of Opioids and Central Nervous System Depressant Drugs".[4] Conclusions from the report were as follows:

- "*Concomitant use of opioids and CNS depressants like benzodiazepines is frequent and potentially harmful. However, they continue to be prescribed together in various clinical conditions. The negative health impact of concomitant use of opioids and CNS depressants has been widely recognized by authorities; and governments, regulators, public payers, and health care professionals' associations have established policies to limit, monitor, or take other actions with respect to the co-prescription of these drugs. This Environmental Scan highlights the policies that are established to reduce the concomitant prescription of opioids and CNS depressants in outpatient settings, in Canada and internationally. The scan also presents the impact of these identified policies, as available*."

- "*Prescribing or dispensing policies, established by public payers in Canada, specific to coprescription of opioids and CNS depressants were not identified. Some standards of practice for health care professionals were identified in Canada, which directed physicians to not prescribe opioids and benzodiazepines concurrently*."

In 2025, British Columbia and other provincial colleges, consider the co-prescription of opioid and benzodiazepine/Z-drugs to be inappropriate and some are monitoring this practice. This is an indication of the harms of opioids plus Z-drugs and benzodiazepines. Lemborexant plus opioid is much safer based on obstructive sleep apnea data. Withholding the only safe sleep medication from the most vulnerable group in society whose lives are in jeopardy is grossly unfair.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Lemborexant would be considered the first-choice option for patients with addictions due to the low addiction liability of the drug. There is no physiological withdrawal with lemborexant and no need to increase the dose to achieve the same outcome. This is not evident with the medications that are currently covered. Lemborexant would also be the first choice for patients undergoing opioid agonist therapy and for those in correctional facilities. In addition, lemborexant should also be a first-line treatment option for very sick patients (e.g., post-cardiac or spinal cord surgery) who have trouble sleeping due to lemborexant's lack of anticholinergic side effects and patients' risk of respiratory depression. Traditionally, hospitalized patients are often prescribed methotrimeprazine or quetiapine but the discharge and recovery process may be sped up in these patients with lemborexant because they can sleep better.

It is not possible to predict which patients will be most likely to respond. Those who respond, respond very well without the need to increase the dose as there is no tolerance. Those with special needs because of the safety profile, would be a priority for use as mentioned above. All patients who are exhibiting an impact on functioning or where insomnia is impacting on their other conditions negatively are the most in need of lemborexant.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

The following outcomes are useful for measuring patients' response to treatment in clinical practice:

- In psychiatry, functional impairment is the most sensitive tool and the patient perspective is paramount. Sleep charts are useful for determining if patients slept but this is not always reliable because patients complain about wanting to sleep better and not feeling rested. Functional improvements (e.g., ability to make lunch for kids and get them to school on time with proper clothing) would be the goal of treatment and is measured through self-report of function, family report, and rating scales (e.g., Epworth, PHQ-9, GAD-7). For example, clinicians treating insomnia ask "How did you wake up?" not "How did you sleep?".
- Patients who use cannabis report it often helps with their sleep. For patients who are prescribed lemborexant for sleep and their cannabis use decreases, this could be a potential marker of efficacy of the insomnia treatment.
- Polysomnography data is important for measuring sleep efficiency.
- Lost prescriptions and frequent refills are evidence of overuse, misuse or diversion especially with benzodiazepines. We do not see evidence of diversion with lemborexant and we do not see the need to increase lemborexant dosage. While lemborexant does not work for all patients, patients do not always need to increase the dose as they do with other insomnia medications. Studies and practice show Lemborexant doesn't cause tolerance.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

If patients report that lemborexant does not work, they are amenable to stopping lemborexant as they don't want to be on it long-term. We do not always observe this with benzodiazepines. Patients wish to stay on benzodiazepines for other reasons (i.e.,

psychological/physiological withdrawal, anxiety management) even when they are not functioning well. This is a critical difference when caring for patients with addictions.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Lemborexant is a medication with proven efficacy and safety. It does not require a specialized setting or a specialist to initiate and monitor response. The fact that it does not show abuse potential or diversion potential in environments that are known for diversion and abuse is reassuring.

6. Additional Information

After having had access to lemborexant for the last four years for our patients with private insurance, we have observed the life changing impact that this insomnia treatment has for many of our patients. Notable observations from our clinical practice include the fact that patients are very satisfied that they fall asleep quickly and they wake up with no drowsiness. Lemborexant has been a successful treatment in many patients suffering from substance use disorders; while we would not treat insomnia with benzodiazepines or Z-drugs in patients with substance use disorders, lemborexant has been an evidence-based therapy alternative that helps avoid the use of off-label drugs such as quetiapine, trazodone and mirtazapine. Lemborexant can be used in high addiction risk patients (i.e., those who are in remission but had severe addiction in the past). This is a major advance in insomnia treatment for this group.

Lemborexant can be safely used in patients with a history of chronic and often severe insomnia, moderate to severe mental illness, or moderate to severe substance use disorders. Many conventional insomnia medications are often ineffective, relatively contraindicated (e.g., sedating antidepressants for a patient with bipolar disorder) or would put patients at risk of harm (i.e., prescribing benzodiazepines or Z-drugs in patients with substance use disorder, especially alcohol, sedative hypnotic use disorder or opioid use disorder). Patients with these disorders report that lemborexant improved sleep, reduced psychiatric and substance use disorder symptoms, provided better daytime function and less distress. Some patients who use smart watches have reported objectively improved sleep quality (within limits of these devices). Lemborexant can be used post-operatively without increased delirium risk.

Lemborexant doesn't work for everyone but, when it does work, it makes a huge difference in patients' lives. Many report "*this is the first time I've been able to sleep in my whole life*" or "*I can enjoy time with my friends and not be tired all day*". With Lemborexant, we can build credibility with addiction patients. Once they report that they are sleeping, we can work with them on reducing their substance use. Tapering patients off benzodiazepines is challenging. They believe they won't sleep. Lemborexant can be used to increase the chance of a successfully withdrawal from benzodiazepines. Patients report "*I can't believe I was stoned all that time*." Patients improved their quality of life by sleeping better and getting off the benzodiazepines. In Corrections, once you treat sleep, patients' benzodiazepine use during day can be reduced. "*Patients believe benzodiazepines are a proper treatment but treating (insomnia) this way is using a Band-Aid solution to cover a fulminant infection. We are not treating what needs to be treated*."

Sadly, lemborexant can be used to effectively manage chronic insomnia in patients that have money or private insurance or coverage through their parents. There is inequity in the system. Patients that can't afford lemborexant are treated differently. Patients that rely on public drug programs are stressed about the cost of lemborexant. Many are on social assistance (e.g., Ontario Works/Ontario Disability Support Program) and simply cannot afford lemborexant. They will rely on family/friends to help cover prescription costs or forgo other crucial items (e.g., groceries, bills, etc.) to pay for their medication. Patients that rely on the public drug programs in Canada also deserve access to an effective and safe treatment for chronic insomnia especially when the patients have comorbid psychiatric conditions.

7. Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   Yes, by Eisai Limited. This was to collate and record all responses from our clinical group. The responses came solely out of our clinical group.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   Yes, please see #1 above. There was no analysis done. Information is from our clinical group. Studies quoted are from Eisai Studies.

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. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Shaohua Lu
Position: Psychiatrist; Clinical Professor, University of British Columbia
Date: 04-04-2025

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

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	X			
Idorsia	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Sam Chang
Position: Clinical Associate Professor, Cummings School of Medicine, University of Calgary
Date: 09-04-2025

☒ 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.

Table 2: Conflict of Interest Declaration for Clinician 2

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		X		
Janssen	X			
Otsuka	X			
Elvium		X		
Takeda		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Timothy Moran, PhD, MD, FRCPC
Position: Physician, Community Mental Health Program; Substance Use and Concurrent Disorders Program Indigenous Program & Department of Psychiatry, Faculty of Medicine, University of Ottawa
Date: 08-04-2025

☒ 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.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Risk Kronfli, MB FRCPC forensic
Position: Clinical Director, ECFH and Correction Health, NS Health; Head, Section of Forensic Psychiatry, Dalhousie University
Date: 06-04-2025

☒ 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.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Nancy Légaré, B.Pharm., M.Sc., Pharm.D., BCPP, BCPS, FOPQ
Position: Docteure en pharmacie Clinique; Professeure adjointe, Départements de psychiatrie et d'addictologie/pharmacologie et physiologie, Faculté de médecine, Université de Montréal; Professeure adjointe, Département de psychiatrie, Faculté de médecine, Université McGill; Coordonnatrice des soins pharmaceutiques, de l'enseignement et de la recherche, Département clinique de pharmacie
Date: 07-04-2025

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai			X	
Otsuka			X	
Lundbeck	X			
Abbvie	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Tin Ngo-Minh
Position: Psychiatrist - Chair of the Community Psychiatry Association of Canada (CPAC)
Date: 04-23-2025

☒ **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.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	X			
Idorsia	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Ravinder S. Mankoo
Position: Psychiatrist, Sleep Specialist
Date: 24-04-2025

☒ 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.

Table 7: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Dr Marie-Helene Geoffroy
Position: General Practionner
Date: 23-04-2025

☒ 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.

Table 8: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai			X	

* Place an X in the appropriate dollar range cells for each company.

REFERENCES

1 Morin CM, Khullar A, Robillard R. Delphi consensus recommendations for the management of chronic insomnia in Canada. Sleep Med 2004;124:598-605.
2 Government of Canada. Health Info Database. Alcohol use among Canadians. Available at: https://health-infobase.canada.ca/alcohol/ctads/. Accessed April 16, 2025.
3 Government of Canada. Health Info Database. Cannabis use (non-medical) in Canada. Available at: https://health-infobase.canada.ca/cannabis/. Accessed April 16, 2025.
4 CADTH. Policies to Prevent Harms from the Co-Prescribing of Opioids and Central Nervous System Depressant Drugs. April 2018. Available at: https://www.cda-amc.ca/sites/default/files/pdf/ES0324_policies_co-prescription_opiods_cns_depressants.pdf. Accessed April 16, 2025.

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Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

Reimbursement Review

Clinician Group Input

Project Number: SR0895-000
Generic Drug Name (Brand Name): Lemborexant (Dayvigo)
Indication: Chronic insomnia
Name of Clinician Group: Aging Patients Clinician Group
Author of Submission: Dr. Ran Liu, Dr. Ashok Krishnamoorthy, Dr. Alan Lowe, Dr. Francois-Gabriel David, Dr. Effie Fanaras, Dr. Raymond Gottschalk, Dr. Marcus Ng, Dr. Sesath Hewapathirane, Dr. Laurel Charlesworth, Dr. Christopher Humphreys, Dr. Armin Rahmani, Dr. Mark Boulos, Dr. Taryn Simms

1. About Your Clinician Group

Our group is comprised of clinicians who specialize in the treatment of older patients (defined as ≥65 years of age).

2. Information Gathering

Information was gathered through discussions on the unmet treatment needs of older patients with chronic insomnia and the potential role of lemborexant to address this.

3. Current Treatments and Treatment Goals

In Canada, both pharmacological and non-pharmacological treatment options are routinely used for the management of insomnia. Non-drug treatments are typically recommended as the first-line option for insomnia and include cognitive behavioural therapy for insomnia (CBT-I), sleep hygiene and/or psychological therapies.[1] Reimbursed pharmacotherapies include benzodiazepine receptor agonists (e.g., lorazepam, clonazepam, temazepam, and alprazolam), non-benzodiazepine-receptor agonists known as Z-drugs, and histamine receptor antagonists.[2] Patients may also receive off-label and/or over-the-counter medications such as antidepressants, antihistamines, antipsychotics, and melatonin.[2] In general, pharmacotherapies currently approved by Health Canada primarily promote sedation and alleviate symptoms of chronic insomnia (such as sleep latency) without addressing the underlying disease mechanism. Beyond approved medications, patients often self-medicate using marijuana, other recreational drugs, herbal substances, and/or alcohol.

Patients ≥65 years of age often experience greater frailty, comorbidity burden, and susceptibility to adverse events (AEs) than younger adults; as such, pharmacological treatments for the management of chronic insomnia in this population should ideally offer consistent and lasting clinical benefits while minimizing safety events. Specifically, medications must effectively improve sleep quality and sleep architecture, facilitate rapid onset of sleep and reduce nighttime awakenings. These treatments also need to minimize residual effects to avoid daytime sedation and resulting cognitive impairment, which is a particular concern for older adults who are at greater risk of such AEs because of age-related changes in brain structure and increasing incidence of neurodegenerative comorbidities. Given the high prevalence of falls among older adults and the potentially serious health consequences this can have, insomnia treatments should be well-tolerated with a low risk of motor-related AEs. Additionally, clinicians and older patients alike have concerns around the use of controlled substances to manage insomnia and are seeking pharmacological treatments that eliminate the potential risk for tolerance, dependence, rebound insomnia, and addiction.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Current treatments reimbursed for insomnia in Canada present numerous limitations for patients aged ≥65 years. This includes their adverse safety profiles which carry substantial risks for older adults. Many benzodiazepine and nonbenzodiazepine sedative hypnotics are associated with residual impairment or "hangover" effect due to their prolonged half-lives. This leads to daytime sedation, along with other side effects such as cognitive impairment, confusion, memory problems, motor incoordination, ataxia, dizziness, and gastrointestinal distress.[3] Older patients may be particularly susceptible to these AEs due to changes in brain structure and drug metabolism associated with aging.[4]

Among the most potentially detrimental side effects of conventional insomnia medications for patients ≥65 years is increased risk of falls and fractures.[4-8] Falls are the leading cause of injury-related deaths among older adults and have a substantial economic burden due to costs associated with fractures, hospital visits, and long-term care. Falls have also been shown to diminish quality of life.[8; 9] Adverse events associated with benzodiazepines and non-benzodiazepine sedative hypnotics such as sedation, dizziness, and impaired cognitive function contribute to a heightened fall risk among older patients with insomnia, with studies showing older adults taking long-term benzodiazepine, zolpidem, or trazodone experienced approximately twice as many falls as those who do not take insomnia medications.[8; 10; 11] In an analysis of more than 1.5 million Medicare beneficiaries, all-cause mortality rates were 15 times higher in older adults treated with earlier generation insomnia medications compared with non-sleep disordered controls. They also had higher adjusted mean number of inpatient, outpatient, and emergency department visits.[8] Notably, insomnia itself has also been linked to increased risk of falls and injury from falling in patients ≥65 years of age.[12; 13] Thus, there is a substantial unmet need for safer, more effective pharmacotherapies to manage chronic insomnia in older patients without further exacerbating the risk of falls.

Many older patients with chronic insomnia have multiple comorbidities that can limit their eligibility for current pharmacotherapies due to potential drug-drug interactions and exacerbation of existing conditions. Conditions like Alzheimer's disease, Parkinson's disease, other forms of dementia, and other neurodegenerative disorders may heighten the sensitivity to cognitive AEs observed with current pharmacotherapies.[14] Therefore, currently approved pharmacotherapies are often not suitable for older patients due to their potential to worsen cognitive impairment and delirium.[15-18]

This leaves older patients with few effective pharmacological options to treat chronic insomnia. While non-pharmacological interventions such as CBT-I are generally recommended for patients aged ≥65 years, accessibility presents a significant barrier to treatment (i.e., lack of availability, insufficient healthcare support, and/or geographical constraints).[2] Additionally, in older patients with many decades of maladaptive behavior forming and/or cognitive impairment, therapy for behavioral modification can be challenging and may not be sufficient to effectively treat chronic insomnia for all patients.

A subset of older patients do not experience adequate improvements in chronic insomnia with currently reimbursed pharmacotherapies, as evidenced by limited improvements in sleep quality and sleep architecture.[7; 19] Further, patients often experience dependance on current agents for sleep and may experience rebound insomnia after discontinuation of treatment, leading to continued reliance on medications beyond the indicated treatment timeframe.

Finally, chronic insomnia is more prevalent among older adults compared to younger populations, likely because of age-related changes in sleep patterns/circadian rhythms and the increased presence of comorbidities such as depression, anxiety, and chronic pain disorders.[20; 21] Older individuals often experience increased sleep fragmentation, with decreases in total sleep, sleep efficiency, deep non-REM (slow wave) sleep and REM sleep.[20] If left untreated, chronic insomnia can lead to significant morbidity in this population, including increased risk of cardiovascular disease and psychiatric conditions, worsening cognitive decline, and diminished quality of life.[7; 15]

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Lemborexant is appropriate as a first-line pharmacotherapy for the treatment of adult patients with chronic insomnia, including those ≥65 years of age, based on its efficacy and a favourable safety profile in clinical trials and real-world practice.[22] Lemborexant has been shown to be beneficial when used alone or in conjunction with frontline non-pharmacological treatments, such as CBT-I, sleep hygiene, and/or other psychological therapies. Coverage of lemborexant would increase the accessibility of pharmacotherapies to

manage chronic insomnia for older patients, as many clinicians avoid prescribing current insomnia medications in this population due to the harmful safety profile.

Beyond its recommendation as a first-line pharmacotherapy, lemborexant would also be the treatment of choice to augment or switch/taper down other sleep agents for patients with severe chronic refractory insomnia who have previously or are currently treated with current pharmacotherapies with limited efficacy and/or adverse events. Lemborexant can be used in combination with existing pharmacotherapies to manage severe refractory insomnia while transitioning down or switching off these therapies.

Lemborexant is effective across the diverse population of aging patients with chronic insomnia, including those with comorbidities such as:

- Sleep apnea, circadian rhythm disorder, and restless leg syndrome (RLS)/periodic limbs movements of sleep (PLMS)
- Psychiatric disorders (e.g., depression, anxiety, post-traumatic stress disorder [PTSD]), schizoaffective disorder, bipolar disorder, schizophrenia, attention deficit hyperactive disorder [ADHD])
- Developmental disorders (e.g., autism), neurodegenerative disorders (e.g,, Alzheimer's disease, Parkinson's disease, and other forms of dementia)
- Neurological diseases (e.g., epilepsy, post-stroke, post-head injury)
- Cardiovascular disorders (e.g., hypertension, chronic heart failure, atrial fibrillation, arrythmia, post myocardial infarct, post cardiac bypass surgery)
- Endocrine disorders (e.g., diabetes, obesity, hypothyroidism)
- Respiratory disorders (e.g., chronic obstructive pulmonary disease [COPD], asthma)
- Autoimmune disorders (e.g., HIV+, hepatitis, Ehlers Danlos syndrome, arthritis, chronic pain, fibromyalgia, osteoarthritis, Sjogren's disease, inflammatory bowel disease [IBD], Crohn's disease)
- Gastroesophageal reflux disease (GERD)

Lemborexant can be safely and effectively used in combination with other medications prescribed to manage these comorbidities.

Studies have supported the safety of lemborexant in patients >65 years old[23] and in patients with dementia.[24] Restless leg syndrome and PLMS increase in prevalence in the elderly population, and can contribute to insomnia-like symptoms. While other sleeping medications can exacerbate RLS, lemborexant is likely safe in RLS and might even be helpful for RLS.[23] Lemborexant can also be safely combined with agents used to manage excessive daytime sleepiness, such as solriamfetol, modafinil, and other wake promoting agents. Lemborexant is safe in sleep apnea and COPD,[25] and this is particularly important for older patients, who have a greater prevalence of respiratory conditions than younger adults

Older patients treated with lemborexant report improvements in sleep quality (as measured by insomnia rating scales), daytime functioning (as measured on scales such as Epworth sleepiness scale, Depression Zimmerman scale, ADLs scales), and work performance (as measured by ADL scales).[22] Sleep studies also indicate lemborexant improves sleep architecture such as increasing rapid eye movement (REM) and non-REM sleep.

One of the key advantages of lemborexant is its favourable safety profile. Compared with currently available pharmacotherapies, older patients treated with lemborexant report lower levels of cognitive impairment, noting they do not experience a 'hangover effect' or fatigue the following day. Further, clinicians have not observed a similar level of long-term dependency with lemborexant, as is often associated with current pharmacotherapies and physicians have been able to successfully discontinue lemborexant treatment. Lemborexant has not been shown to be associated with rebound insomnia, withdrawal symptoms, overdose, or abuse, allowing long-term treatment as needed to resolve chronic insomnia. Clinicians in this group have not reported any seizures (including withdrawal seizures) with lemborexant and there has been no worsening of seizure activity among those with epilepsy. Patients have also reported reductions or discontinuation of alcohol, drugs, and marijuana previously used as self-medication.

Overall, the introduction of lemborexant would shift the current treatment paradigm, allowing clinicians to avoid first-line use of controlled substances currently used for chronic insomnia. Lemborexant is not associated with time duration limitations, allowing patients to receive consistent treatment until they achieve remission.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Lemborexant is suitable for patients aged 18 years and older with chronic insomnia. Lemborexant has been shown to be well-tolerated among older adults, including those with comorbidities, and can be safety integrated into existing medication regimens, most notably in patients with neurocognitive comorbidities such as Parkinson's disease, Alzheimer's disease, and other forms of dementia. In some cases, improvements in sleep may lead to enhanced daytime function and reduced risk of delirium among patients with neurocognitive comorbidities. This is striking when compared to conventional pharmacotherapies for insomnia which pose an increased risk of falls and serious injury in the same vulnerable populations. Some insomnia patients have also reported improvements in daytime headaches with lemborexant, while others with chronic disorders have reported reductions in pain.

In more challenging environments, lemborexant can be particularly beneficial for the management of insomnia in older adults and patients with dementia in inpatient, palliative care, and long-term care settings. These patients often experience greater cognitive frailty, with more polypharmacy and numerous comorbidities. Poor sleep in such environments can easily lead to delirium, drastically increasing the risk of falls, mortality, and healthcare cost. Evidence suggests lemborexant is associated with significantly lower rates of delirium and falls in the inpatient setting compared to conventional insomnia medications.[26-31]

The only contraindication for lemborexant is narcolepsy.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Treatment outcomes with chronic insomnia are subjective, with a reliance on patient-reported outcomes to determine response. For aging patients, this may include self-reported outcomes and insights from their caregivers, families, and/or healthcare providers. This may include changes in baseline measures related to sleep quality and quantity (e.g., insomnia severity index, Epworth sleepiness scale), daytime function, ADLS, mental clarity, work performance and quality of life.[32] Given the subjective nature of the outcomes, clinicians need to educate patients to set appropriate expectations for response to pharmacotherapy. The tolerability of the treatment should also be considered, as assessed by discontinuation rates of currently available pharmacotherapies and/or self-medication with marijuana, drugs, and alcohol.

Potential qualitative evidence to evaluate the clinical meaningfulness of lemborexant for chronic insomnia in the aging population may include large longitudinal database studies on lemborexant use and outcomes (i.e., including discontinuation data, risk of hospitalizations, adverse events, etc.), primary care database studies on any association of lemborexant use with falls, pharmacy data on discontinuation of other sleeping agents/medications, and long-term comparative data for patients with insomnia treated with lemborexant versus benzodiazepines and zopiclone.

Hospital and care facilities can also assess older patients treated with lemborexant for rates of delirium, falls, medical complications (i.e., cardiovascular and respiratory), and mortality compared to other insomnia medications. Cost saving analysis comparing lemborexant to existing pharmacotherapies for the treatment of insomnia may also be useful and should consider the comprehensive cost of insomnia in older patients and patients with dementia, including reducing falls, medical resources for treatment of complications, reducing caregiver costs, reduced injury, and burnout to staff.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Patients ≥65 years of age have reported successfully discontinuing lemborexant treatment after their sleep cycles were restored (i.e., they felt they no longer needed medication to regulate sleep). Unlike current pharmacotherapies used to manage insomnia, there is no clear withdrawal or rebound insomnia observed with lemborexant discontinuation. Some patients have reported daytime sleepiness, nightmares, and vivid dreams with lemborexant; however, in general, patients report much better tolerance compared with existing insomnia medications. Discontinuation of treatment should be based on joint patient-physician decisions, weighing the benefit with the potential risks.

Lemborexant has been shown to provide early clinical benefits, with early onset of sleep improvements reported in night 1 and night 2 of treatment in phase 3 clinical trials and real-world experience of older patients.[22] Despite the rapid potential benefits, continued usage of lemborexant for 2-4 weeks may further enhance the treatment effect; as such, clinicians recommend it should be used consistently until patients have achieved complete remission for several weeks to months to prevent relapse (depending on insomnia severity), especially in those with chronic severe refractory insomnia. In addition to improving sleep quality, likely with continued usage, there is improvement in patients' behaviour around sleep, such as keeping a consistent sleep routine and improved day time function, which over time may also contribute to insomnia remission. Patients should report improvements in both sleep

quality/quantity and daytime functioning followed by persistent stable outcomes before considering dose modification, schedule modifications, or discontinuation. Concomitant use of non-pharmacotherapies such as CBT-I and mindfulness programs with lemborexant may also be beneficial to prevent relapse, although it is noted that such programs may not be appropriate for older patients with cognitive impairment (i.e., due to neurodegenerative diseases and/or medications).

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Lemborexant is appropriate for the treatment of insomnia across a range of settings, including outpatient, long-term care facilities, palliative facilities, and inpatient settings (including in medical and psychiatry wards). A specialist is not routinely required to diagnosis, treat, or monitor patients who might receive lemborexant for insomnia. If other sleep disorders are suspected that may contribute to sleep impairment, we recommend referral to a sleep medicine specialist.

6. Additional Information

Our clinician group would like to share our first-hand experience of the impact that lemborexant has had on managing chronic insomnia for older adults.

Benefits of lemborexant include the fact that lemborexant has a much better safety profile compared to older generation insomnia medications, and this is especially important for elderly patients and patients with dementia, who are more cognitively fragile, have higher rates of insomnia, and have more medical and psychiatric comorbidities and are on more medications. Many patients report clearly feeling better the next day after switching onto lemborexant from an older sleeping medication. Lemborexant can be helpful in the inpatient setting when poor sleep may induce delirium in patients who are at baseline cognitively fragile. Finally, older patients have better sleep quality with lemborexant.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CDA-AMC 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 clinician group input. CDA-AMC may contact your group with further questions, as needed. Please see the *Procedures for Drug Reimbursement Reviews* for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   Eisai held a virtual advisory board meeting during which some of the questions in this submission were discussed. The content of the submission was later directed only by the authors and we were provided with assistance in the form of medical writing support if needed.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   See above.

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. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Ran Liu MD, FRCPC, DABPN, DABSM, CSCN (EEG), MSc
Position: Physician (Neurologist, Sleep Medicine Specialist)
Date: 23-04-2025

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai				X
Jazz		X		
Paladin		x		
Takeda	X			
Sunovion	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Ashok Krishnamoorthy
Position: Dept Head,Psychiatry, Richmond,BC
Date: 01-04-2025

☒ 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.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Lundbeck	X			
EISAI		X		
ABBVIE	X			
Sanofi	X			
Jannssen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Alan David Lowe, BScPhm, MD, FRCPC
Position: Psychiatry/ Neuropsychiatry/ Sleep Medicine; Assistant Professor of Psychiatry

Date: 07-04-2025

☒ 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.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: François-Gabriel David, B. Sc., MD, CCFP, DTM
Position: MD
Date: 24-04-2025

☒ 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.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
GSK	X			
AZ	X			
Novo Nordisk	X			
Pfizer	X			
Otsuka	X			
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Effie Fanaras
Position: Respirology and Sleep Medicine; Medical Director, Medsleep
Date: 24-04-2025

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Marcus C. Ng, BMSc, MD(STIR), FRCPC, CSCN(EEG)
Position: Associate Professor of Neurology / Epileptologist
Date: 29-04-2025

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Table 6: Conflict of Interest Declaration for Clinician 6

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				X
Paladin				X

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Dr. Sesath Hewapathirane
Position:
Date: 29-04-2025

☒ 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.

Table 7: Conflict of Interest Declaration for Clinician 7

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	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Dr. Raymond Gottschalk
Position: Consultant

Date: 29-04-2025

☒ 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.

Table 8: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai			X	
Palladin	X			
Jazz	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Laurel Charlesworth MD FRCPC
Position: Neurologist & Sleep Medicine Specialist, The Ottawa Hospital
Date: 29-04-2025

☒ 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.

Table 9: Conflict of Interest Declaration for Clinician 9

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: Dr. Christopher Humphreys, MD, FRCPC, DRCPSC
Position: Respirology and Sleep Medicine; Medical Director, Toronto Grace Hospital Sleep Lab
Date: 29-04-2025

☒ 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.

Table 10: Conflict of Interest Declaration for Clinician 10

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 11

Name: Dr. Armin Rahmani
Position: Psychiatrist, Sleep Medicine Specialist
Date: 29-04-2025

☒ 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.

Table 11: Conflict of Interest Declaration for Clinician 11

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 12

Name: Dr. Mark Boulos

- Position: Staff Neurologist (Stroke & Sleep), Sunnybrook Health Sciences Centre
- Associate Professor, University of Toronto
- Senior Scientist, Sunnybrook Research Institute
- Medical Lead, Sunnybrook Sleep Laboratory
- Sleep Neurology Fellowship Program Director, University of Toronto
- Field Editor, *Sleep Medicine*

Date: 29-04-2025

☒ 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.

Table 12: Conflict of Interest Declaration for Clinician 12

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 13

Name: Dr. Taryn Simms MD, FRCPC

Position: Physician (Respirology and Sleep Medicine)
Date: 29-04-2025

☒ 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.

Table 13: Conflict of Interest Declaration for Clinician 13

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

REFERENCES

1 Morin CM, Khullar A, Robillard R, Desautels A, Mak MSB et al. (2024) Delphi consensus recommendations for the management of chronic insomnia in Canada. *Sleep Medicine* 124 598-605.
2 CADTH (2020) Clinical Evaluation of Interventions for the Management of Insomnia: A Review of Reviews. *CADTH Technology Review* 10
3 Holbrook AM, Crowther R, Lotter A, Cheng C, King D (2000) Meta-analysis of benzodiazepine use in the treatment of insomnia. *Cmaj* 162 (2): 225-233.
4 Samara MT, Huhn M, Chiocchia V, Schneider-Thoma J, Wiegand M et al. (2020) Efficacy, acceptability, and tolerability of all available treatments for insomnia in the elderly: a systematic review and network meta-analysis. *Acta Psychiatr Scand* 142 (1): 6-17.
5 Bain KT (2006) Management of chronic insomnia in elderly persons. *Am J Geriatr Pharmacother* 4 (2): 168-192.
6 Scharner V, Hasieber L, Sönnichsen A, Mann E (2022) Efficacy and safety of Z-substances in the management of insomnia in older adults: a systematic review for the development of recommendations to reduce potentially inappropriate prescribing. *BMC Geriatr* 22 (1): 87.
7 Molnar F, Frank C, Chun S, Lee EK (2021) Insomnia in older adults: Approaching a clinical challenge systematically. *Can Fam Physician* 67 (1): 25-26.
8 Amari DT, Juday T, Frech FH, Wang W, Wu Z et al. (2022) Falls, healthcare resources and costs in older adults with insomnia treated with zolpidem, trazodone, or benzodiazepines. *BMC Geriatrics* 22 (1): 484.
9 Bergen G, Stevens MR, Burns ER (2016) Falls and Fall Injuries Among Adults Aged ≥65 Years - United States, 2014. *MMWR Morb Mortal Wkly Rep* 65 (37): 993-998.
10 de Jong MR, Van der Elst M, Hartholt KA (2013) Drug-related falls in older patients: implicated drugs, consequences, and possible prevention strategies. *Ther Adv Drug Saf* 4 (4): 147-154.
11 Díaz-Gutiérrez MJ, Martínez-Cengotitabengoa M, Sáez de Adana E, Cano AI, Martínez-Cengotitabengoa MT et al. (2017) Relationship between the use of benzodiazepines and falls in older adults: A systematic review. *Maturitas* 101 17-22.
12 Noh JW, Kim KB, Lee JH, Lee Y, Lee BH et al. (2017) Association between Sleep Duration and Injury from Falling among Older Adults: A Cross-Sectional Analysis of Korean Community Health Survey Data. *Yonsei Med J* 58 (6): 1222-1228.
13 Jiang Y, Xia Q, Wang J, Zhou P, Jiang S et al. (2019) Insomnia, Benzodiazepine Use, and Falls among Residents in Long-term Care Facilities. *International Journal of Environmental Research and Public Health* 16 (23): 4623.
14 He Q, Chen X, Wu T, Li L, Fei X (2019) Risk of Dementia in Long-Term Benzodiazepine Users: Evidence from a Meta-Analysis of Observational Studies. *J Clin Neurol* 15 (1): 9-19.
15 Patel D, Steinberg J, Patel P (2018) Insomnia in the Elderly: A Review. *Journal of Clinical Sleep Medicine* 14 (06): 1017-1024.
16 Lenzer J (2005) FDA warns about using antipsychotic drugs for dementia. *BMJ* 330 (7497): 922.
17 Pottie K, Thompson W, Davies S, Grenier J, Sadowski CA et al. (2018) Deprescribing benzodiazepine receptor agonists: Evidence-based clinical practice guideline. *Can Fam Physician* 64 (5): 339-351.
18 American Geriatrics Society Beers Criteria Update Expert Panel (2019) American Geriatrics Society 2019 Updated AGS Beers Criteria(R) for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc* 67 (4): 674-694.
19 Chun S, Lee EK (2016) INSOMNIA IN THE ELDERLY: UPDATE ON ASSESSMENT AND MANAGEMENT. *Canadian Geriatrics Society* 6 (1):
20 Ohayon MM, Carskadon MA, Guilleminault C, Vitiello MV (2004) Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep* 27 (7): 1255-1273.

21 Mookerjee N, Schmalbach N, Antinori G, Thampi S, Windle-Puente D et al. (2023) Comorbidities and Risk Factors Associated With Insomnia in the Elderly Population. *J Prim Care Community Health* 14 21501319231168721.
22 Gotfried MH, Auerbach SH, Dang-Vu TT, Mishima K, Kumar D et al. (2024) Efficacy and safety of insomnia treatment with lemborexant in older adults: analyses from three clinical trials. *Drugs Aging* 41 (9): 741-752.
23 Arnold V, Ancoli-Israel S, Dang-Vu TT, Mishima K, Pinner K et al. (2024) Efficacy of Lemborexant in Adults >/= 65 Years of Age with Insomnia Disorder. *Neurol Ther*
24 Moline M, Thein S, Bsharat M, Rabbee N, Kemethofer-Waliczky M et al. (2021) Safety and Efficacy of Lemborexant in Patients With Irregular Sleep-Wake Rhythm Disorder and Alzheimer's Disease Dementia: Results From a Phase 2 Randomized Clinical Trial. *J Prev Alzheimers Dis* 8 (1): 7-18.
25 Cheng JY, Lorch D, Hall N, Moline M. Respiratory safety of lemborexant in adult and elderly subjects with moderate-to-severe chronic obstructive pulmonary disease. J Sleep Res. 2025;34:e14334.
26 Ogura T, Ueno S, Okuda A, Nishioka N, Miyano A et al. (2022) Can Lemborexant for Insomnia Prevent Delirium in High-Risk Patients with Pancreato-Biliary Disease after Endoscopic Procedures under Deep Sedation? *J Clin Med* 12 (1):
27 Matsuoka A, Sogawa R, Murakawa-Hirachi T, Mizoguchi Y, Monji A et al. (2023) Evaluation of the delirium preventive effect of dual orexin receptor antagonist (DORA) in critically ill adult patients requiring ventilation with tracheal intubation at an advanced emergency center: A single-center, retrospective, observational study. *Gen Hosp Psychiatry* 83 123-129.
28 Matsuoka A, Tobita S, Sogawa R, Shinada K, Murakawa-Hirachi T et al. (2022) Evaluation of Suvorexant and Lemborexant for the Prevention of Delirium in Adult Critically Ill Patients at an Advanced Critical Care Center: A Single-Center, Retrospective, Observational Study. *J Clin Psychiatry* 84 (1):
29 Henmi R, Nakamura T, Mashimoto M, Takase F, Ozone M (2024) Preventive Effects of Ramelteon, Suvorexant, and Lemborexant on Delirium in Hospitalized Patients With Physical Disease: A Retrospective Cohort Study. *J Clin Psychopharmacol* 44 (4): 369-377.
30 Hirata R, Katsuki NE, Shimada H, Nakatani E, Shikino K et al. (2024) The Administration of Lemborexant at Admission is Not Associated with Inpatient Falls: A Multicenter Retrospective Observational Study. *Int J Gen Med* 17 1139-1144.
31 Sogawa R, Emoto A, Monji A, Miyamoto Y, Yukawa M et al. (2022) Association of orexin receptor antagonists with falls during hospitalization. *J Clin Pharm Ther* 47 (6): 809-813.
32 Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M (2008) Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults. *Journal of Clinical Sleep Medicine* 04 (05): 487-504.

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Reimbursement Review

Clinician Group Input

Project Number: **SR0895-000**
Generic Drug Name (Brand Name): DAYVIGO (lemborexant)
Indication: Chronic Insomnia
Name of Clinician Group: Alberta Psychiatrists
Author of Submission: Drs. Manrit Kaur Takhar, Thomas Stark, Parker Dahl, Patricia Maron, Noura Al Faraj, Lisa Harpur, Amanda Berg, Sylvia Mousa, Martin Vetter

1. About Your Clinician Group

Our group consists of Alberta psychiatrists who treat patients with insomnia with and without psychiatric comorbidities, with a focus on improving daily function and quality of life with long-term solutions. Our experience and opinions represent the treatment of all ages of patients from adolescents to older individuals.

2. Information Gathering

Information was gathered initially through an advisory board consultation with Alberta psychiatrists to gain insight into our collective clinical experience with insomnia treatments. We discussed the current management of patients with insomnia, with and without psychiatric comorbidities, as well as how DORAs may fit into the treatment landscape. The discussions were transcribed and shared with other psychiatrists from Alberta and the questions below were answered utilizing the output of the discussions.

3. Current Treatments and Treatment Goals

Non-drug treatments are the preferred option for insomnia treatment. The most studied treatment is cognitive behavioural therapy for insomnia (CBT-I), a psychotherapeutic approach involving different techniques including sleep restriction, stimulus control therapy, education on sleep hygiene practices, and cognitive therapy.

It should be noted that most of the evidence available to support the efficacy of CBT-I has been collected through studies of patients that do not have concurrent psychiatric disorders. When patients have comorbid psychiatric disorders, there is a much higher likelihood that pharmacological options will be needed to treat the insomnia. Moreover, pharmacological therapy can be considered alongside CBT-I as it may produce faster improvements in sleep than CBT-I alone.

Currently approved pharmacotherapies for insomnia include benzodiazepine receptor agonists (flurazepam, nitrazepam, triazolam, and temazepam), Z-drugs (zopiclone, zolpidem, and eszopiclone), histamine receptor agonists (doxepin), and dual orexin receptor antagonists (lemborexant and daridorexant; DORAs), each targeting different mechanisms. For example, DORAs reduce wakefulness, while benzodiazepines and Z-drugs promote sedation.

Patients may also receive non-prescription or over-the-counter medications, such as antihistamines, antinauseants, valerian, St John's wort, melatonin, L-tryptophan. Some patients self-medicate using alcohol. Several classes of pharmaceuticals are used off-label in some patients, including anxiolytics (clonazepam and lorazepam), antidepressants (mirtazapine, trazodone, amitriptyline, and nortriptyline), atypical antipsychotics (quetiapine), and anticonvulsants (gabapentin and pregabalin).

The ideal treatment for insomnia should have rapid onset, improve sleep architecture; and enhance daytime functioning without causing daytime sedation, cognitive impairment, or rebound insomnia. It must be non-addictive, safe for long-term use, well-tolerated

across diverse populations (including elderly and those with comorbid conditions), cost-effective, and covered by insurance, with no significant drug interactions or fall risk.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

In addition to the high cost and limited access to CBT-I treatment, a subset of individuals do not respond to CBT-I therapy. Some estimates suggest that 40% of those referred for individual and group CBT-I will drop out before mid-treatment. Further, as noted in question 3 above, patients having chronic insomnia concurrent with psychiatric disorders also have a much higher likelihood of requiring pharmaceutical treatment because the CBT-I is not sufficient to achieve treatment success.

Many mental health disorders, such as chronic pain, post-traumatic stress disorder (PTSD), mood and anxiety disorders, attention deficit hyperactive disorder (ADHD), and addictions, are associated with sleep disorders. Improving sleep through the treatment of insomnia can lead to improvements in these comorbid conditions. However, medications for insomnia raise concerns due to side effects such as daytime sedation, memory and motor deficits, respiratory issues, rebound insomnia, complex sleep behaviors, and the development of tolerance and/or dependence. Over-the-counter and off-label treatments can cause additional side effects, including nausea, fatigue, and drowsiness, which negatively affect day-to-day functioning, productivity, and overall quality of life.

Many pharmacological medications are controlled substances and pose risks of abuse, addiction, and withdrawal. This is particularly troublesome for individuals with a history of addiction. There is ample data suggestive of risks for cross addiction when patients are treated with benzodiazepine agents or Z-drugs when there is a co-occurring addiction to the insomnia disorder. This problem not only occurs in cases of pre-existing addiction, but both medication classes are notorious in regard to the development of tolerance and dependence on their own. This is compounded by a well-documented side effect profile for rebound insomnia in those treated with those agents for longer periods of time, making the medications difficult to withdraw, even when they affect the safety of a patient.

Moreover, older generation insomnia medications, such as benzodiazepines, trazodone, and zolpidem, are associated with an increased risk of falls, which is especially concerning for aging or frail patients. Additionally, some of these medications can exacerbate cognitive impairment and delirium, posing particular risks for older patients with neurodegenerative disorders like Alzheimer's disease. Thus, the current options pose significant risks for many populations of individuals requiring pharmacotherapy for insomnia.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Insomnia is very commonly comorbid in many mental health conditions such as depression, anxiety, ADHD and trauma. Moreover, sufficient and restorative sleep is required for the optimal treatment of all mental health disorders. Finally, impaired sleep can itself result in the development of mental illness or exacerbate mental illness symptoms. For example, there is a well-known bidirectional relationship between insomnia and alcohol abuse. Oftentimes, insomnia results in patients self-treating via alcohol use and alcohol addiction is known itself to impair sleep architecture and quality. Thus, a cycle repeats such that without addressing the insomnia, the use behaviours persist.

DORAs are currently recommended as a first-line pharmacotherapy for patients with insomnia as they have proven efficacy, a more favourable safety profile and preserve patients' ability to function. DORAs have been approved by Health Canada for the treatment of both sleep onset and sleep maintenance insomnia. Most importantly, a unique property associated with DORAs is that the literature suggests they improve daytime functioning. It is this quality that sets them apart from other agents and provides for a robust indication when they are used in the treatment of insomnia.

As mentioned, many of the medications currently approved by Health Canada result in well-known risks for dependence, tolerance and addiction. DORAs are unique in this regard. They are specifically approved for insomnia, and they don't appear to share these risks. It appears as though this relates to a unique mechanism of action that other medications do not target, the orexin system. It is thought that due to this unique mechanism of action, DORAs appear to be able to be used in the long term without the development of tolerance and dependence.

Various real-world evidence and retrospective studies suggest that DORAs offer notable benefits for patients with insomnia, particularly those with psychiatric comorbidities. Moreover, unlike trazodone, zolpidem, or benzodiazepines, DORAs carry a lower risk of falls, introducing a medication class that is safe to use in the elderly, as this population does exhibit a higher risk for the development of poor sleep or insomnia,

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

DORAs are appropriate for patients with insomnia, including those with comorbid psychiatric disorders and various non-psychiatric medical conditions. Research indicates that DORAs not only improve insomnia but also help reduce cognitive symptoms, such as delirium, in adults with comorbid non-psychiatric conditions, while also alleviating depressive symptoms in older adults with insomnia. Overall, DORAs have been demonstrated to be well-tolerated in patients with and without various comorbidities and can be safely added to existing medication regimens or used as part of a tapering process to discontinue/reduce treatments like hypnotics. In the clinical setting, DORAs have demonstrated a consistent response and have particularly proven effective for individuals with new-onset insomnia, as well as for elderly patients. Additionally, unlike controlled substances (e.g., benzodiazepines and Z-drugs) or other insomnia medications (e.g., hypnotics, trazodone, and diphenhydramine), DORAs carry very low real-world abuse and dependence risks, making them a preferable treatment option for patients with a history of addiction and other mental health disorders.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Given the subjective nature of several treatment outcomes for insomnia, there is a strong reliance on patient-reported outcomes and surveys, each with varying levels of significance. However, measurable outcomes are also used across studies. Key qualitative and quantitative outcomes considered in clinical practice include the following:

- Daytime fatigue
- Cognitive performance
- Falls risk
- Driving safety
- Respiratory safety
- Abuse potential; tolerance and dependence
- Sleep onset/maintenance
- Sleep quality
- Functional outcomes (e.g., daytime functioning, abnormal thoughts/behaviour, daytime dizziness/grogginess)
- Effect on psychiatric and non-psychiatric comorbidities

The importance of assessing next-day functioning cannot be overstated, with patients' mental clarity having a direct impact on their daily activities, driving, and ability to work, study, and uphold various responsibilities. Measures of presenteeism (e.g., productivity) and absenteeism (i.e., missed days of work) can be used to help quantify the potential economic benefits of treatment as well. Furthermore, it is important to consider outcomes that are meaningful to patients, which can vary substantially. For example, one study of over 600 participants found that patients preferred improved daytime functioning from a sleep medication over the total hours of sleep.[1]

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Clinicians may consider switching a medication if a patient experiences impaired daytime functioning, balance or memory issues, reduced cognitive function, or other prominent side effects. Since DORAs may take 2-4 weeks to show their full effect, clinicians recommend consistent use to achieve optimal results. In clinical observations, next-day fatigue was noted to be somewhat higher with lemborexant compared to daridorexant, another DORA, and a small subset of patients (1-2%) experienced sleep paralysis,

[1] Heidenreich S, et al. *Sleep*. 2022;45:zsac204

although it is uncommon. Some patients have also reported nightmares and vivid dreams with lemborexant (as compared to daridorexant which do not appear to have the same REM promoting effects).

DORAs should be discontinued or closely monitored if a patient begins treatment with a moderate or strong CYP3A inhibitor. Co-administration of DORAs with CYP3A inducers may reduce the efficacy of DORAs.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

DORAs are suitable for use in both inpatient and outpatient settings. DORAs, including lemborexant and daridorexant, are prescribed by physicians; however, in Alberta, pharmacists are authorized to prescribe DORAs to patients. Clinicians encourage pharmacist education programs to extend therapy and improve patient care, allowing pharmacists to monitor symptoms in place of physicians. However, the lack of coverage for DORAs often leads many prescribers to choose Z-drugs, despite the risks, or results in the patients self-medicating with street drugs.

6. Additional Information

A study of 948 adults estimated the total annual cost of insomnia to be $6.6 billion in Québec, including direct costs such as healthcare consultations, medications, and alcohol used as a sleep aid. Individuals with insomnia incur an average annual cost of $5,010, compared to $421 for good sleepers.[2] They also miss an average of 10 workdays per year, compared to 3 for those without insomnia, and experience 28 days of lost productivity annually, compared to just 3 days for good sleepers. Furthermore, individuals with insomnia are almost twice as likely to experience non-driving-related accidents (odds ratio: 2.43). These notable financial and productivity losses underscore the urgent need for safe and effective insomnia treatments to improve both individual health outcomes and reduce the broader economic burden.

Good quality sleep is an essential human need and the inability to sleep well must be adequately addressed. The current treatment options don't permit patients to perform and be alert the next day. Amongst clinicians, there is a recognition that, when there are issues with sleep, they must be addressed in order to be able to address patients' other mental health challenges. When you look at a patient's natural history and development issues, insomnia is often at the core. If the insomnia could have been addressed earlier, we may be able to avert resultant mental health issues, and the downstream economic costs described above. If clinicians have a tool to treat insomnia that is efficacious, safe, and can be used long term, we may be able to avoid the development or worsening of mental health conditions.

Finally, not only does a lack of quality sleep affect individuals, it also impacts a family unit especially if family members are in a caregiver role (i.e., for children or dependent adults). Given DORAs unique symptom target around improved daytime functioning of the patient, the family and the society is able to benefit when used for insomnia treatment. With proper treatment of insomnia, individuals can resume their studies, resume taking care of their family and improve or maintain employment opportunities through better cognitive performance.

7. Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   See question 2 below.

2 Daley M. et al. *Sleep.* 2009:32:55-64

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   The physician group who authored this document collated information compiled through an EISAI funded ad-board organized in the month of March 2025. Following the ad-board meeting, EVERSANA provided medical writing assistance to compile the responses to each question independent of EISAI. The authors of this submission had full control over the content of this submission.

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. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Thomas Stark
Position: Psychiatrist
Date: 28-04-2025

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	x			
Otsuka	x			
Johnson & Johnson	x			
Boehringer Ingelheim	x			
Abbvie	X			
Kye	X			
Elvium	X			
HLS Therapeutics	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Manrit Kaur Takhar
Position: Psychiatrist
Date: 28-04-2025

☒ 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.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Otsuka		X		
Eisai		X		
Janssen	X			
Abbvie	X			
Lundbeck	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Parker Dahl
Position: Psychiatrist
Date: 28-04-2025

☒ 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.

Table 3: Conflict of Interest Declaration for Clinician 3

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	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Patricia Maron
Position: Psychiatrist
Date: 28-04-2025

☒ 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.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Alberta Health and Wellness				X

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Noura Al Faraj
Position: Psychiatrist
Date: 28-04-2025

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Lisa Harpur
Position: Psychiatrist
Date: 28-04-2025

☒ **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.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Amanda Berg
Position: Psychiatrist
Date: 28-04-2025

☒ 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.

Table 7: Conflict of Interest Declaration for Clinician 7

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Otsuka	X			
Eunoia Medical	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Sylvia Mousa
Position: Psychiatrist
Date: 28-04-2025

☒ 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.

Table 8: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Martin Vetter
Position: Psychiatrist
Date: 28-04-2025

☒ 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.

Table 9: Conflict of Interest Declaration for Clinician 9

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Elvium	X			
Otsuka	X			
Kye	X			
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: Nathan Finkbeiner

Position: Physician
Date: 27-04-2025

☒ 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.

Table 10: Conflict of Interest Declaration for Clinician 10

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Otsuka	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 11

Name: Inga Smit
Position: Psychiatrist
Date: 28-04-2025

☒ **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.

Table 11: Conflict of Interest Declaration for Clinician 11

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Otsuka	X			
Lundbeck	X			
Abbvie	X			
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 12

Name: Helen Yeung
Position: Psychiatrist
Date: 28-04-2025

☒ 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.

Table 12: Conflict of Interest Declaration for Clinician 12

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
None				

* Place an X in the appropriate dollar range cells for each company.

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Reimbursement Review

Clinician Group Input

Project Number: SR0895-000
Generic Drug Name (Brand Name): Lemborexant (DAYVIGO)
Indication: Chronic Insomnia
Name of Clinician Group: Chronic Insomnia Clinician Group
Authors of Submission: Drs. Atul Khullar, Sophie Mazur, Michael Mak, Wayne Wei-ku Lai, Marie Josée Filteau, Liu Liu, James MacFarlane, Chris McRee, Wilfred Jerome Alonso, David J. Robinson, Keith Thompson, Diane McIntosh, Manisha Witmans, Larry J. Klassen, Stephan Brennan, Omar Din, Lemore Alima

1. About Your Clinician Group

This is a group of healthcare practitioners (HCPs), including primary care, psychiatry and long-term care professionals. This clinician group is comprised of a network of senior clinicians from across Canada who have a very strong interest in the treatment of chronic insomnia.

This group also includes regionally and nationally known specialist and family physician experts in the clinical management of sleep disorders in clinical practice across Canada and the world.

There are hundreds of years of multi-disciplinary clinical experience among this group treating chronic insomnia in many populations. Clinicians in this group also represent a wide variety of treatment settings, including university, community, long-term care, hospital, as well as private outpatient settings. Many are involved in the development of guidelines and are active in research, and most are keenly interested in the evolution of education and better clinical practice.

2. Information Gathering

Our group was assembled for the purpose of providing input for this submission. Our conversations related to the limitations of the current treatment alternatives, the assessment of meaningful response to treatment in our clinical practice, and the place in therapy of lemborexant were documented and then used to populate this template.

3. Current Treatments and Treatment Goals

Insomnia is a significant health concern in Canada, impacting as many as 18.1% of men and 29.5% of women[1] with an estimated 16.3% of patients experiencing chronic insomnia (commonly characterized by symptoms lasting for 3 months or longer[2,3]) and, of those, 14.7% seek regular pharmaceutical therapy.[2] Chronic insomnia can substantially impair quality of life and ability to function in the workplace or fulfil societal responsibilities.[4] As such, chronic insomnia

imposes a substantial burden for patients, their families, and society overall, with estimated total costs of $1.9 billion in 2021, accounting for 1.9% of all illness-associated costs in Canada.[1] The 2024 Delphi consensus recommendations for the management of chronic insomnia in Canada unanimously concluded that the burden of chronic insomnia is substantial and should not be underestimated.[5] As such, the importance of providing an effective and safe treatment for patients with chronic insomnia cannot be overstated.

Chronic insomnia possesses a bi-directional relationship with several other common comorbid conditions, such as anxiety, depression, addiction, cardiometabolic disorders, and aging-related conditions; however, the 2024 Delphi consensus recommendations specify that insomnia should be specifically targeted for treatment even in the presence of comorbidities (100% consensus).[5] The primary goal of this targeted treatment is to provide effective relief of chronic insomnia while minimizing adverse effects. The ideal treatment would provide good quality sleep and produce favorable next-day functioning. Treatments currently used in Canada for insomnia include the Z-drugs (zolpidem, zopiclone, eszopiclone), benzodiazepine receptor agonists (e.g., lorazepam, diazepam, alprazolam) and other off-label treatments including antihistamines, melatonin, antidepressants (such as trazodone), antipsychotics (quetiapine), gabapentin and pregabalin. Substances misused by patients include tetrahydrocannabinol (THC) and alcohol. Most of the treatments are not approved by Health Canada for use in insomnia or are approved by Health Canada for short-term use only (i.e., up to 10 days at a time). The Z-drugs contain Black Box warnings for respiratory depression and complex sleep-related behaviours; benzodiazepines have Black Box warnings for addiction, abuse, misuse, withdrawal, and risk of concomitant use with opioids. Of the Z-drugs, only zopiclone is reimbursed in some jurisdictions. Many of the other treatment options are reimbursed for long term use despite the safety warnings.

Currently reimbursed and non-reimbursed therapies act as sedatives and do not target the underlying cause of the condition. Moreover, the proposed Canadian treatment algorithm indicates that most currently available agents have safety concerns or an unclear or hazardous safety and efficacy profile.[4] Overall, the consensus guidelines emphasize the importance of drugs, such as lemborexant, that provide benefits that outweigh any risks associated with long-term treatment and improve sleep architecture.[4] Lastly, although cognitive behavioural therapy for insomnia (CBT-I) is also offered as a non-pharmacologic treatment option, use is limited due to significant barriers related to accessibility, lack of efficacy for some patients, challenges in compliance for certain patients[5] and, per our clinical observation, inability to engage in CBT-I for patients who are too unwell and require a pharmaceutical treatment first.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

There is an overarching need for therapies that are proven efficacious and are indicated for use in chronic insomnia that clinicians can feel confident in prescribing (i.e., with a favorable risk/benefit profile). Appropriate therapies would promote next day functioning, and have a favorable long-term efficacy and tolerability. Novel therapies are needed that address the underlying chronic insomnia, rather than targeting symptoms or comorbid conditions, by working in a central, natural fashion. As not all patients respond to available treatments, as many treatments as possible are needed that are effective for chronic insomnia and that work long-term. Further, there is a need for better tolerated therapies.

Current treatments are often ineffective at relieving chronic insomnia and are associated with daytime somnolence/sedation/fatigue. Treatments are limited in their ability to provide long-term relief of chronic insomnia, and many agents treat the comorbid issues rather than the underlying sleep condition. Given that chronic insomnia often necessitates treatment over the long-term, many available treatments pose a high risk of tolerance, as well as addiction/dependency and withdrawal symptoms. In addition, current treatments pose a high risk for adverse events

and drug-drug interactions. Most treatments are associated with limited or low-quality evidence and some products may have poor quality control. In addition, many currently used treatments are not indicated and/or not reimbursed for chronic insomnia. Self-medication with substances among patients with chronic insomnia is common,[5] with options such as alcohol potentially worsening sleep and alcohol/cannabis producing negative next-day side effects. Overall, the limitations associated with currently available treatments not only preclude safe and effective treatment of chronic insomnia, but they may also exacerbate existing comorbidities. The current state of public reimbursement of pharmaceutical treatment for chronic insomnia in Canada is not grounded in evidence-based medicine nor does it represent quality patient care.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Lemborexant should be used as a first-line pharmacotherapy for patients with chronic insomnia. Lemborexant offers an important treatment alternative for patients who currently present with sleep-related complaints and may have experienced weeks, months, or years of ongoing sleep challenges despite trying numerous therapies (including over the counter options or non-pharmaceutical interventions). With lemborexant, patients report improvements in sleep quality, daytime functioning, and work performance. Sleep studies also indicate lemborexant improves sleep architecture, such as increasing both rapid eye movement (REM) and non-REM (NREM) sleep.

It is the opinion of our clinician group that the only reason to choose another molecule over lemborexant is the current lack of financial reimbursement. As clinicians, we must consider reimbursed options when prescribing treatments to patients, which means that offering the best available therapy is often not an option.

Although there is an option to administer CBT-I prior to initiating pharmacotherapy with lemborexant for those that are well enough, access to psychological treatments is often prohibited by location (limited availability outside of major treatment centers, which are accessible only to a minority of patients), high costs, limited patient receptiveness to psychological intervention, limited efficacy and/or impaired timeliness of treatment (wait times can be up to two years).[5] In such cases of limited access, lemborexant may help to avoid delays in treatment by providing a bridge to CBT-I (given that lemborexant can be safely tapered and even discontinued without evidence of rebound insomnia[6,7]); in other cases, lemborexant may circumvent the need for CBT-I altogether.

In the current treatment paradigm, clinicians are highly reluctant to prescribe existing treatment options such as benzodiazepines due to their associated safety risk and may avoid these agents entirely. Dual orexin receptor antagonists (DORAs) such as lemborexant are considered practice-changing, as clinicians will have greater comfort and confidence prescribing a treatment with an improved risk profile compared to other publicly funded drugs. Lemborexant poses a lower risk of polypharmacy and drug-drug interactions and is simple to use and suitable for patients with a wide range of comorbidities.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Lemborexant should be used in patients with chronic insomnia. Lemborexant may be of particular interest for patients who need to be focused the next day without any secondary effects of drowsiness or brain fog as lemborexant improves sleep architecture. Patients who perform shift work or have to get up frequently in the night (e.g., young mothers, people on call) also report improved sleep and daytime performance with lemborexant. Notably, a recent systematic literature review and meta-analysis found that lemborexant was the only option with no statistically or clinically significant effect on driving performance or premature driving test termination.[8] Lemborexant should also be considered for patients with chronic insomnia who are unable to access CBT-I or whose chronic insomnia persists after receiving CBT-I. This medication would also be ideal for older adolescents.

Considering the widespread prevalence of chronic insomnia in Canada,[2] the benefits of lemborexant are anticipated to be far-reaching. Among patients with chronic insomnia, those with comorbidities (e.g., anxiety, depression, addictions, cardiometabolic disorders, and aging-related conditions) are well-suited to receive lemborexant and lemborexant has been shown to be efficacious in patients with comorbidities.[9] A recent Canadian study revealed that insomnia affects a diverse patient population but is most common among individuals reporting comorbidities or impaired physical/mental health, as well as among women and Indigenous persons.[2] Given the existing marginalization often faced by these groups in Canada, failure to reimburse a safe and effective treatment option for chronic insomnia results in further marginalization and we have seen it worsen their comorbidities. In contrast, lemborexant appears effective and safe for treating insomnia associated with comorbid psychiatric disorders.[9-12]

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

This clinician group has seen wide ranging improvement in a number of clinically meaningful outcomes for both patients and clinicians. A key outcome of interest among patients with chronic insomnia is daytime functioning/next-day functioning. For instance, we have noticed that next-day functioning is a clear indicator of the benefits of lemborexant over most other agents, with patients reporting that they can be fully functioning with lemborexant but patients often avoiding driving the next day with other agents. Patients should be questioned in detail and in a consistent manner about their sleep at each follow-up. The goal of this questioning is to quantify and qualify sleep (e.g., awakening and "returns") and next-day functioning (i.e., patients' impression of fatigue or restfulness during the day and whether they feel refreshed in the morning). Disability and work scales can be used to provide quantitative evaluations. Specific scales of interest include insomnia rating scales and activities of daily living (ADL) scales, which provide opportunities to assess sleep quality, daytime functioning, and work performance. Clinicians have seen improvement in these scales when used clinically. These types of subjective outcomes of sleep usually predict functional outcomes better than the objective outcomes in clinical practice.

It is important to consider outcomes that are meaningful to patients with chronic insomnia, which can vary substantially across specific patient subgroups depending on demographics and comorbid conditions, but generally relate to improved sleep quality and next-day functioning and reduced side effects compared to other therapeutic options. The breadth of outcomes that may be relevant to different patient comorbidity populations include the potential to avoid side effects (particularly those that may exacerbate existing comorbidities), appropriate sleep/waking, ability to maintain daily routines, and ability to fulfil familial and social obligations.[12]

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Among patients suffering from chronic insomnia, the use of lemborexant may be short term or regular/ongoing, depending on patients' treatment goals (i.e., as-needed for symptom relief versus as an effort to restore sleeping patterns). Notably, although remission data are not yet available, some patients with chronic insomnia appear to no longer require lemborexant after a finite treatment duration of two to three months, suggesting that a proportion of patients may not require lemborexant indefinitely.[12,13]

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

The diverse population of patients suffering from chronic insomnia is well-aligned with the broad spectrum of settings and prescribers appropriate for lemborexant use. Lemborexant is suitable for use in both inpatient and outpatient settings. A lack of fall risk and safety/tolerability makes lemborexant a particularly advantageous treatment in the

inpatient setting. Lemborexant can be prescribed by a general practitioner, primary care health care provider or a specialist.

6. Additional Information

It is our opinion that the prior recommendation for lemborexant contained rationale that was contradictory and not clinically relevant. For example, efficacy should be the primary outcome measure. Efficacy is the goal of registration trials and the reason for approval of lemborexant by Health Canada, the Food and Drug Administration and the European Medicines Agency. Patient Reported Outcomes (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. Nevertheless, new real-world studies suggest that lemborexant is efficacious in patients with comorbidities as described above.

From the recommendation, 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.[15] These were both met for the most part by lemborexant in Sunrise 1 and 2.[7,12] 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/anxietysubgroup. 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 and zopiclone are very comparable clinically as they are of the same drug class and have a shared mechanism,[16] 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.[17] 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." The additional further clear data showing the safety of lemborexant is compelling. 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 is simply not put into context. Even though the reduction of fall risk can't be conclusively noted, the signal for postural stability[17] 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.[18,19] 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,[20,21] the effect size is diminished with anxiety,[22] CBT-I compliance is poor with comorbidities[23] 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.[24] 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.**

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.[25] 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.

Our clinician group would also like to share our personal accounts of the success we have seen when treating patients with lemborexant, grouped by key themes:

Key Themes	Representative Personal Account
Earlier and More Effective Treatment	• "lemborexant allows me to treat more insomnia patients, more effectively, earlier." • "lemborexant has allowed patients to have more effective consistent treatment earlier in insomnia journey." • "With lemborexant, memory, balance, and restorative sleep are better." • "I have seen lemborexant put the chronic insomnia in remission after a few months in many patients."
Improved Safety and Ability to Taper Z-drugs and benzodiazepines	• "lemborexant enables sparing of more toxic treatments and self-medication." • "I was able to wean patients off of Z-drugs and benzodiazepines who had been taking them for several years." • "lemborexant permits other medications to be stopped and often puts the chronic insomnia into remission after several months." • "Patients are no longer on Z-drugs and are sleeping well without the need for drug escalation of Z-meds!" • "A 57-year-old lawyer had struggled with sleep issues and struggled for many years, seeing many sleep experts in the process. The patient was on very high doses of zopiclone and zolpidem (~9 tablets a day). With lemborexant use, the patient was able to reduce their Z-drug usage."

Increased Quality of Life and Restoration of Normal Sleep Architecture	• "Many patients with chronic insomnia have lifechanging improvement in mood, daytime function and quality of life, now that lemborexant offers a safe and effective medication helps them sleep." • "Patients find back their ability to dream. Patients have full sleep architecture." • "It [lemborexant] has lived up to its claim of being very safe and effective overall and displaying what it has shown in clinical trials in terms of sleep architecture improvements such as increasing REM and NREM sleep which I have observed on sleep studies with patients reporting better sleep and daytime functional outcomes."
Improved Productivity and Reduced Social Stigma	• "Patients have been able to get back to work and their lives." • "lemborexant is associated with much less stigma." • "I had a 72-year-old patient two weeks ago terminal /palliative cancer telling me that lemborexant was the only sleep medication that provided him with predictable calm sleep and that he didn't feel guilty taking it as he knew he would be "present" the next day and be able to be with his family without feeling groggy and lost. He wished that he would have had lemborexant earlier in his life as he chronically struggled with insomnia and struggled to function at work the next morning." • "I have seen improved ability to reduce alcohol and cannabis intake with the use of lemborexant."

7. Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   Yes. Our group had the support of a medical writer that documented our discussions and input them into the template. The medical writer was funded by Eisai Canada. Eisai was not involved in any fashion in developing the content of this submission.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   Not applicable.

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. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Atul Khullar
Position: Clinical Associate Professor, University of Alberta Dept of Psychiatry
Date: 29-04-2025

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie/Allergan		X		
Idorsia			X	
Otsuka		X		
Lundbeck		X		
Jazz Pharma		X		
Paladin Pharma	X			
Takeda	X			
Bausch Health			X	
Eisai		X		
Elvium			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Sophie Mazur MD
Position: Clinique Priveo Santé
Date: 04-07-2025

☒ 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.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai, Idorsia, Elvium, Takeda, Novo Nordisk and Astellas	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Michael Mak
Position: Sleep Physician
Date: 04-07-2025

☒ 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.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai				X
Idorsia			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Wayne Wei-ku Lai
Position: Medical Director for Kelowna General Hospital Sleep Lab and Clinical Assistant Profession at UBC
Date: 25-04-2025

☒ 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.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Marie Josée Filteau
Position: Psychiatrist
Date: 24-04-2025

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Abbvie	X			
Eisai	X			
HLS Therapeutics	X			
Lundbeck	X			
Otsuka	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Liu Liu
Position: Family Physician
Date: 25-04-2025

☒ 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.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: James MacFarlane
Position: Director; MedSleep
Date: 24-05-2025

☒ 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.

Table 7: Conflict of Interest Declaration for Clinician 7

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Idorsia		X		
Eisai		X		
Paladin		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Chris McRee
Position: Clinical Pharmacist - Psychiatry - Grey Nuns Community Hospital, Edmonton, AB
Date: 24-04-2025

☒ 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.

Table 8: Conflict of Interest Declaration for Clinician 8

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Otsuka	X			
Lundbeck	X			
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Wilfred Jerome Alonso, MD
Position: Medical Director, Canadian Sleep Consultants; Clinical Assistant Professor, Cumming School of Medicine, University of Calgary
Date: 24-05-2025

☒ 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.

Table 9: Conflict of Interest Declaration for Clinician 9

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Apnimed			X	
Eli Lilly	X			
Axsome	X			
Idorsia			X	
Paladin Labs	X			
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: David J. Robinson MD, FRCPC
Position: Psychiatrist, London ON
Date: 29-04-2025

☒ 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.

Table 10: Conflict of Interest Declaration for Clinician 10

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			x	
Otsuka			x	
Lundbeck		x		
Janssen		x		
AbbVie		x		
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 11

Name: Dr Keith Thompson
Position: Family Physician London, Ontario
Date: April 25, 2025

☒ 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.

Table 11: Conflict of Interest Declaration for Clinician 11

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
NuraLogix	X			
Idorsia Pharmaceutical	X			
GSK Pharmaceutical	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 12

Name: Diane McIntosh, MD, FRCPC
Position: Psychiatrist and Chief Neuroscience Officer
Date: 25-04-2025

☒ 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.

Table 12: Conflict of Interest Declaration for Clinician 12

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AbbVie	x			
Lundbeck	x			
Otsuka	x			
Janssen Ortho	x			
Eisai	x			
Idorsia	x			
Indivior	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 13

Name: Manisha Witmans, MD, FRCPC, FAASM
Position: Sleep Medicine Physician; Associate Clinical Professor, University of Alberta; ACESO Medical
Date: 28-04-2025

☒ 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.

Table 13: Conflict of Interest Declaration for Clinician 13

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 14

Name: Larry J. Klassen, MD, FRCPC
Position: Research Chair, Eden Mental Health Centre
Date: 25-04-2025

☒ 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.

Table 14: Conflict of Interest Declaration for Clinician 14

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AbbVie		x		
Eisai	x			
Elvium		x		
Idorsia	x			
Kye		x		
Lundbeck	x			
Otsuka	x			
Takeda		x		
Vectura Fertin Pharma	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 15

Name: Dr. Stefan Brennan
Position: Psychiatrist, Professor, Department of Psychiatry, University of Saskatchewan
Date: 29-04-2025

☒ 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.

Table 15: Conflict of Interest Declaration for Clinician 15

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Otsuka		X		
AbbVie		X		
Janssen-Ortho	X			
Takeda	X			
Lundbeck	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 16

Name: Dr. Omar Din
Position: Psychiatrist
Date: 28-04-2025

☒ **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.

Table 16: Conflict of Interest Declaration for Clinician 16

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 17

Name: Lemore Alima MD
Position: Physician, Northern Alberta Sleep Clinic
Date: 29-04-2025

☒ 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.

Table 17: Conflict of Interest Declaration for Clinician 17

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None		X		

* Place an X in the appropriate dollar range cells for each company.

References

1. Chaput JP, Janssen I, Sampasa-Kanyinga H, Carney CE, Dang-Vu TT et al. (2023) Economic burden of insomnia symptoms in Canada. *Sleep Health* 9 (2): 185-189.
2. Morin CM, Vézina-Im L-A, Chen S-J, Ivers H, Carney CE et al. (2024) Prevalence of insomnia and use of sleep aids among adults in Canada. *Sleep Medicine* 124 338-345.
3. Dopheide JA (2020) Insomnia overview: epidemiology, pathophysiology, diagnosis and monitoring, and nonpharmacologic therapy. *Am J Manag Care* 26 (4 Suppl): S76-s84.
4. Clarke K, Orlov N, Soong C (2024) Treatment of chronic insomnia in adults. *Canadian Family Physician* 70 (3): 176.
5. Morin CM, Khullar A, Robillard R, Desautels A, Mak MSB et al. (2024) Delphi consensus recommendations for the management of chronic insomnia in Canada. *Sleep Med* 124 598-605.
6. Karppa M, Yardley J, Pinner K, Filippov G, Zammit G et al. (2020) Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2. *Sleep* 43 (9):
7. Rosenberg R, Murphy P, Zammit G, Mayleben D, Kumar D et al. (2019) Comparison of lemborexant With Placebo and Zolpidem Tartrate Extended Release for the Treatment of Older Adults With Insomnia Disorder: A Phase 3 Randomized Clinical Trial. *JAMA Netw Open* 2 (12): e1918254.
8. McElroy H, O'Leary B, Adena M, Campbell R, Tahami Monfared AA et al. (2021) Comparison of the effect of lemborexant and other insomnia treatments on driving performance: a systematic review and meta-analysis. *Sleep Adv* 2 (1): zpab010.
9. Katsuta N, Takahashi K, Kurosawa Y, Yoshikawa A, Takeshita Y, Uchida Y, et al. Safety and real-world efficacy of lemborexant in the treatment of comorbid insomnia. Sleep Medicine: X: 2023.
10. Mishima K, Fujimoto K, Endo A, Ishii M. Safety and efficacy of lemborexant in insomnia patients: Results of a postmarketing observational study of Dayvigo® tablets. Drugs R D. 2024;24(2):211-26.
11. Horikoshi S, Miura I, Suzuki Y, Kobayashi Y, Hirata Y, Goto M, et al. Switching to lemborexant for the management of insomnia in mental disorders: The SLIM study. J Clin Sleep Med. 2023;19(10):1753-8.
12. Roth T, Rosenberg R, Morin CM , Yardley J, Pinner K, Perdomo C. Impact of lemborexant treatment on insomnia severity: analyses from a 12-month study of adults with insomnia disorder. Sleep Medicine 2022;90: 249-257.
13. Tanaka-Mizuno S, Fujimoto K, Mishima K, Sakata Y, Fukasawa T, Mizuno K, et al. Evaluation of prescribing patterns of switching to and add-on lemborexant in patients treated with hypnotic medication: a nationwide claims database study in Japan. Expert Opin Pharmacother. 2024;25(12):1707-16.
14. Chepke C, Cote KA, Pinner K, Yardley J, Lundwall C, Moline M. Effect of lemborexant on daytime functioning in adults with insomnia: patient-reported outcomes from a Phase 3 clinical trial. Prim Care Companion CNS Disord 2025;27.
15. Morin CM, Belleville G, Belanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep. 2011 May;34(5):601-608. doi:10.1093/sleep/34.5.601

16. Nutt DJ, Stahl SM. Searching for perfect sleep: the continuing evolution of GABAA receptor modulators as hypnotics. J Psychopharmacol. 2010 Nov;24(11):1601-12. doi: 10.1177/0269881109106927. Epub 2009 Nov 26.
17. Moline M, Zammit G, Yardley J, Pinner K, Kumar D, Perdomo C, Cheng JY. Lack of residual morning effects of lemborexant treatment for insomnia: summary of findings across 9 clinical trials. Postgrad Med. 2021 Jan;133(1):71-81. doi: 10.1080/00325481.2020.1823724. Epub 2020 Oct 29. PMID: 33119423
18. Takkouche B, Montes-Martínez A, Gill SS, Etminan M. Psychotropic medications and the risk of fracture: a meta-analysis. Drug Saf. 2007;30(2):171-84. doi: 10.2165/00002018- 200730020-00006. PMID: 17253881.
19. Seppala LJ, Wermelink AMAT, de Vries M, et al; EUGMS Task and Finish Group on Fall-RiskIncreasing Drugs. Fall-risk-increasing drugs: a systematic review and meta-analysis, II: psychotropics. J Am Med Dir Assoc. 2018;19(4):371.e11-371.e17.
20. Trauer JM, Qian MY, Doyle JS, Rajaratnam SM, Cunnington D. Cognitive Behavioral Therapy for Chronic Insomnia: A Systematic Review and Meta-analysis. Ann Intern Med. 2015 Aug 4;163(3):191-204. doi: 10.7326/M14-2841. PMID: 26054060.
21. Harvey AG, Tang NK. Cognitive behaviour therapy for primary insomnia: can we rest yet? Sleep Med Rev. 2003 Jun;7(3):237-62. doi: 10.1053/smrv.2002.0266. PMID: 12927123.
22. Belleville G, Cousineau H, Levrier K, St-Pierre-Delorme MÈ. Meta-analytic review of the impact of cognitive-behavior therapy for insomnia on concomitant anxiety. Clin Psychol Rev. 2011 Jun;31(4):638-52. doi: 10.1016/j.cpr.2011.02.004. Epub 2011 Feb 17. PMID: 21482322
23. Chan NY, Chan JWY, Li SX, Wing YK. Non-pharmacological Approaches for Management of Insomnia. Neurotherapeutics. 2021 Jan;18(1):32-43. doi: 10.1007/s13311-021-01029-2. Epub 2021 Apr 5. PMID: 33821446; PMCID: PMC8116473
24. Morin CM, Bélanger L, LeBlanc M, Ivers H, Savard J, Espie CA, Mérette C, Baillargeon L, Grégoire JP. The natural history of insomnia: a population-based 3-year longitudinal study. Arch Intern Med. 2009 Mar 9;169(5):447-53. doi: 10.1001/archinternmed.2008.610. PMID: 19273774
25. Sharma V, Simpson SH, Samanani S, Jess E, Eurich DT. Concurrent use of opioids and benzodiazepines/Z-drugs in Alberta, Canada and the risk of hospitalisation and death: a case cross-over study. BMJ Open. 2020 Nov 20;10(11).

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

Reimbursement Review

Clinician Group Input

Project Number: SR0895-000
Generic Drug Name (Brand Name): Lemborexant (Dayvigo)
Indication: Chronic Insomnia
Name of Clinician Group: Cardiometabolic Patient Clinician Group
Author of Submission: Dr. James Kim, Dr. Jennifer Swainson, Dr. RJ Kamatovic, Dr. Alexandro Zarruk, Dr. Abdeltif Benhaddad, Dr. Raymond Gottschalk, Dr. Jon Chan, Dr. Barry Goldenberg, Dr. Roger Bashala, Mr. Rick Siemens, Dr. Nazli Parast, Dr. Shahebina Walji

1. About Your Clinician Group

This group is comprised of clinicians with interests both in management of cardiometabolic conditions and the concurrent treatment of insomnia. The group includes psychiatrists, internists, family physicians, and obesity medicine specialists.

2. Information Gathering

The group assembled with the purpose of discussing the opportunity to provide input into the review of lemborexant in chronic insomnia. Specifically, issues around the current standards of care and their limitations, the place in therapy of lemborexant, the outcomes used in clinical practice to evaluate response to treatment and our experience with lemborexant were discussed. A first draft was prepared based on the discussions and then all group participants contributed to the final version.

3. Current Treatments and Treatment Goals

Cognitive behavioural therapy for insomnia (CBT-I), is the first line treatment. This is a multimodal intervention that may combine both behavioural and cognitive techniques such as sleep hygiene, sleep restriction, stimulus control, sleep education, and relaxation therapies.[1] Though CBTi is first line, it does not work for all patients due to a lack of specialized CBT-I therapists, and many patients are unable or unwilling to do it so pharmacotherapy is often recommended in parallel. This could be considered similar to advising patients with diabetes about diet and exercise, but also prescribing diabetes medications.

Pharmacotherapy for chronic insomnia includes both on- and off-label treatments. On-label treatment options include benzodiazepines (e.g., temazepam and triazolam), Z-drugs, sedating antidepressants (low dose doxepin) and now the dual orexin receptor antagonists (DORAS) – daridorexant and lemborexant. As the benzodiazepines and Z-drugs are recommended only for short-term use, off-label prescribing is common in treatment of chronic insomnia. These off-label options include sedating antidepressants (mirtazapine, trazodone, amitriptyline), atypical antipsychotics (quetiapine, olanzapine), and anticonvulsants (gabapentin, pregabalin). These treatments currently address the symptoms of chronic insomnia but do not target the underlying disease mechanism and carry a heavy potential side effect burden including weight gain with atypical antipsychotics and memory impairment and motor impairment with the benzodiazepines (and Z drugs other than Zolpidem (which has a higher prevalence of sleep related behaviours such as sexsomnia and sleepwalking which has medicolegal implications)).

The key therapeutic goals of treatment for chronic insomnia are to improve sleep quality ensuring patients can maintain high daytime functioning. These treatments should also be well-tolerated, with minimal adverse events. Recently, clinical guidelines have also begun to recognize the intersection between sleep and cardiometabolic health, with the 2022 American Heart Association (AHA) guidelines updated to include sleep health as one of the eight essential components of cardiovascular health. This update reflects growing recognition that sleep is closely linked to other key components of cardiovascular health, including healthy weight, blood

pressure, and blood lipid and glucose levels. This is especially relevant for individuals with cardiometabolic disease, as they face an elevated risk of worsening symptoms and disease progression as a result of insufficient or poor-quality sleep.[2-5] Conversely, cardiometabolic issues can exacerbate sleep disturbances, further supporting the bidirectional relationship between insomnia and cardiometabolic disease. Reflecting this, the 2021 Canadian Cardiovascular Society Guidelines identify sufficient sleep duration as a primary prevention strategy for dyslipidemia, a major risk factor for cardiovascular disease (CVD).[6] Similarly, recent government guidelines from British Columbia highlighted sleep as an important component of overall diabetes care and management, supported by Diabetes Canada guidelines for pediatric patients and a retrospective study showing that treating sleep disturbances may help to reduce type 2 diabetes risk.[7-13]

Overall, the ideal treatment for insomnia would provide effective and sustained relief without exacerbating existing cardiometabolic conditions and would present a favourable risk-benefit profile for long-term use. Currently reimbursed pharmacotherapies do not target the underlying cause of insomnia and may even promote cardiometabolic disease progression. As a result, many patients continue to experience poor sleep quality, alongside the potential worsening of their comorbid conditions.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Treatments are needed for chronic insomnia that do not carry risk of cardiometabolic complications (i.e., such as weight gain, increases in lipid, glucose, and blood pressure levels) that are seen with commonly used off-label medications for insomnia. Obstructive sleep apnea (OSA) is a common comorbidity with insomnia and cardiometabolic disease and many existing sleep medications may exacerbate this condition. As such, medications that are safe in patients with comorbidities such as OSA are needed.

Goals for chronic insomnia that are not being met by currently available options include the requirement for treatments that address the underlying mechanism of the disease, rather than just the symptoms. Patients need to be able to function the next day and not be impaired. Current pharmacotherapies such as benzodiazepine receptor agonists manage the acute symptoms of chronic insomnia but not the underlying disorder. Patients often develop tolerance to these therapies, providing patients with transient, short-term benefits that often diminish prior to achieving remission. Once these acute medications have been ruled out, patients with chronic insomnia have limited treatment options that support long-term use. Benzodiazepine receptor agonists and Z-drug therapies have not been shown to improve sleep architecture and may suppress rapid eye movement (REM) sleep and slow wave sleep which is currently felt to increase glymphatic flow in the brain and reductions in glymphatic flow dysfunction is associated with neurodegenerative disorders such as Alzheimer's disease.[14] These pharmacotherapies are also commonly associated with daytime sedation, next day functional impairment, and drowsiness, and may have extended adverse event profiles. These effects are further compounded in individuals with cardiometabolic disease, who face additional challenges related to their underlying condition(s). For example, benzodiazepines have been associated with dependency, respiratory depression, a prolonged QT interval, increased myocardial ischemia, and a worsened prognosis in patients with CVD, with some of these effects directly contributing to the onset of sudden cardiac arrest.[10]

Recent consensus guidance on chronic insomnia management in Canada note that most available agents present potential safety concerns or have an unclear or hazardous safety and efficacy profile.[15] Among these, benzodiazepines are particularly concerning for individuals with cardiometabolic disease. Despite their widespread use, benzodiazepines have been linked to serious adverse outcomes, including a higher risk of sudden cardiac arrest in a cohort of over 74,000 patients with CVD,[10] and an 80% increase in heart disease-related mortality in a meta-analysis.[11] Population-based studies have also found that benzodiazepine use increased the risk of OSA—an effect contrary to the goal of improving sleep.[12] OSA itself disrupts appetite-regulating mechanisms, promoting increased food intake and potential weight gain or difficulties losing weight, an especially concerning issue for individuals with obesity.[13] Moreover, OSA is a prevalent comorbidity among individuals with type 2 diabetes, with an estimated overall prevalence of up to 90%.[16] Despite these risks, benzodiazepines remain the most prescribed sleep medication for patients with type 2 diabetes.[12-16] Some evidence also suggests that long-term use of benzodiazepines may impair glycemic control, adding to the potential risks for individuals with type 2 diabetes.[17] Considering that physical activity plays a key role in the day-to-day maintenance of glycemic control,[18] benzodiazepine use may impair physical performance by reducing muscle strength and balance, effectively hindering individuals' ability to engage in regular exercise necessary for diabetes and/or weight management.[19,20] Notably, these impairments have been shown to rapidly improve following the discontinuation of benzodiazepines.[19] Other medications, such as histamine receptor agonists and off-label antidepressants, can lead to weight gain, which may be a particular issue for patients with obesity or

other cardiometabolic disorders. According to Obesity Canada guidelines, disrupted sleep can contribute to challenges with weight management.[21] Addressing sleep disturbances may therefore play an important role in supporting healthier weight regulation and improving overall cardiometabolic health.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Lemborexant should be considered appropriate as a first-line pharmacotherapy for patients with chronic insomnia, as it targets the underlying pathology to restore natural sleep cycles and increase sleep quality by reducing sleep latency, improving sleep continuity and improved both sleep onset and maintenance insomnia. It is not associated with dependence, drug diversion or tolerance. The SUNRISE 2 trial identified safety in those up to 88 years old with efficacy persisting at 12 months with no rebound on discontinuation of the medication. It is suitable for patients with comorbid cardiometabolic conditions, offering clinical benefits to a variety of patient populations, including those with comorbidities who may not be suitable candidates for current pharmacotherapies. By improving sleep quality and quantity, lemborexant may help to manage cardiometabolic disorders and is not associated with adverse outcomes that may worsen cardiometabolic health, nor does it have known contraindications with medications commonly used to treat cardiometabolic conditions. Patients with any form of primary insomnia could benefit from lemborexant treatment and may be particularly well-suited for those with initial onset of primary insomnia as it minimizes exposure to current pharmacotherapies associated with addiction, impaired daytime functioning, drowsiness, and other safety concerns. This is especially important for individuals with obesity and/or type 2 diabetes, as they can benefit from increased energy and ability to exercise during the day, without fatigue interfering with their physical activity and daily functioning.

The bidirectional relationship between sleep disturbances and cardiometabolic disease necessitates a safe and effective treatment to improve sleep (thereby benefiting cardiometabolic health) while minimizing risks to cardiometabolic health.[4] Sleep deprivation impairs glucose metabolism and promotes insulin resistance, appetite, risk of weigh gain/obesity, elevated blood pressure, inflammation, and oxidative stress—all of which are key factors in the development of hypertension and atherosclerosis.[2] Additionally, sleep disorders are recognized risk factors for worsening cardiovascular function, including coronary heart disease, heart failure, and CVD. In patients with heart failure, sleep disturbances are linked to a higher risk of ventricular arrhythmias requiring surgical intervention. In patients with CVD undergoing cardiac surgery, sleep disorders, particularly OSA, significantly increase the risk of postoperative cognitive dysfunction, including delirium (odds ratio [OR]: 6.4, 95% CI: 2.6, 15.4, $P < 0.001$). This risk may be further compounded by zolpidem, a commonly prescribed Z-drug for sleep disturbances. These concerns underscore the need for lemborexant as an effective and well-tolerated alternative that improves sleep without worsening underlying cardiometabolic conditions, ultimately supporting overall health improvement. Unlike currently available pharmacotherapies, patients treated with lemborexant have achieved deep REM sleep and stage 3 sleep. Lemborexant offers a more favourable safety profile than current pharmacotherapies for chronic insomnia and is not associated with cardiometabolic or respiratory complications. It would be a perfect complement to cognitive therapies that would improve sleep hygiene and behaviours but fail to address the underlying pathology of neurotransmitter excitability that lemborexant would target.

Given that chronic diseases are the leading contributors to the overall burden of illness costs in Canada, with type 2 diabetes alone being the most expensive in 2021 at $754 million, reimbursement of lemborexant is recommended to ensure its first-line use for chronic insomnia.[22] Lemborexant is expected to shift the current treatment paradigm for chronic insomnia in Canada and is preferred by our clinician group over current pharmacotherapies.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Lemborexant is appropriate for patients with chronic insomnia, including those with cardiometabolic disease. Reimbursement of lemborexant will allow clinicians to reduce patients' use of sedative drugs that often have very harmful side effects. Additional risks linked to self-medicating with alcohol, particularly its association with increased cardiovascular risk, can also be mitigated.[23] Lemborexant can be effective for patients who have failed to respond to current pharmacotherapies or could not tolerate these medications due to the associated adverse events, an especially important consideration for those with underlying cardiometabolic disease, given the risks of ischemic heart disease from benzodiazepines and increased mortality from coronary artery disease linked

to hypnotics, both of which are commonly prescribed for sleep disturbances.[11] Lemborexant can be used across diverse patient populations, including those with obesity/overweight and diabetes.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Clinical response to lemborexant should be assessed using patient-reported measures for daytime function and quality of life scales. The insomnia severity index (ISI) should also be used before and after treatment to assess changes in insomnia severity and impact. While other scales may provide additional information, they can be more time-intensive than the ISI and may therefore not be feasible in a busy community practice. Metabolic fitness can also be indicative of sleep quality; as such, response to lemborexant may be demonstrated by reductions in insulin resistance, obesity-related morbidities, diabetes, and atherosclerotic heart disease (ASHD). Additional data should be collected to evaluate lemborexant's ability to improve cardiometabolic conditions, or at the very least to confirm it does not worsen existing ones.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Unlike other currently available treatments for insomnia, discontinuing treatment with lemborexant is not anticipated to negatively impact patients' physical or mental wellbeing, even in the presence of comorbid cardiometabolic conditions. In both pivotal trials (Study 1, NCT02952820 and Study 2, NCT02783729), no evidence of rebound insomnia was observed, indicating that patients could safely discontinue lemborexant without experiencing withdrawal symptoms or a deterioration in sleep patterns.[24-26]

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Lemborexant may be administered in any clinical setting, including by family physicians in the community setting. Unlike some other currently used treatments, lemborexant is easy and safe to prescribe, with no titration needed and minimal risk of side effects, overdose, or dependency.

6. Additional Information

Public reimbursement of lemborexant will enable clinicians to readily provide patients with the most efficacious and well-tolerated available treatment, removing funding restrictions and circumventing the need to prescribe older, less desirable options with a negative safety profile.

Our experience with lemborexant on the lives of our patients with cardiometabolic issues has revealed a positive effect of lemborexant on targeted fat loss (i.e., weight loss without muscle loss). In addition, some patients with diabetes have lost weight, been able to reduce blood pressure medications, have better moods, and generally be more productive. With availability of DORAs, it's possible to use a DORA for chronic insomnia where patients are less likely to gain weight and develop metabolic dysfunction.

7. Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

EVERSANA helped with the medical writing of this document under the direction of the clinician group. Our group had full autonomy over the content presented.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

As above.

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. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: James Kim, MBBCh, PgDip(Diabetes), MScCH(HPTE), CPC(HC)
Position: Clinical Assistant Professor, Dept of Family Medicine, University of Calgary
Date: 04-04-2025

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AstraZeneca, Eli Lilly, Janssen, Otsuka, Searchlight	X			
Abbott, AbbVie, Bayer, Boerhinger-Ingelheim, embecta, GSK, Pfizer, Teva		X		
Eisai, embecta, Novo Nordisk			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Jennifer Swainson, MD, FRCPC, Diplomate, American Board of Obesity Medicine
Position: Associate Clinical Professor, Dept of Psychiatry, University of Alberta
Date: 05-04-2025

☒ 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.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai			X	
Idorsia		X		
Bausch	X			

Novo nordisk	X			
Otsuka		X		
AbbVie			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: RJ Kamatovic
Position: Family Medicine, Fort Erie, Ontario
Date: 08-04-2025

☒ 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.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
NovoNordisk	X			
Eli Lilly	X			
Boehringer Ingelheim	X			
Astra Zeneca	X			
Bausch	X			
GSK	X			
Pfizer	X			
Lundbeck	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. A. Ben Haddad, M.D., MSc
Position: <Enter currently held position>
Date: 25-04-2025

☒ **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.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
GSK	X			

AstraZeneca	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Raymond Gottschalk
Position: Consultant
Date: 25-04-2025

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai			X	
Palladin	X			
Jazz	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Jonathan Chan
Position: Founder & Director, The Sleep Institute Ltd.; Founder & Director, Imagine Health Centres Ltd.
Date: 25-04-2025

☒ 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.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Dr. Barry Goldenberg, M.D.
Position: Family Physician
Date: 24-04-2025

☒ 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.

Table 7: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Dr. Alexandro Zarruk
Position: M.D.
Date: 27-04-2025

☒ 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.

Table 8: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eli Lilly		x		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Dr. R. Bashala, MD, LMCC, CFP
Position: Montreal General & Royal Victoria Hospital - MUHC
Date: 24-04-2025

☒ 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.

Table 9: Conflict of Interest Declaration for Clinician 9

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: Rick Siemens
Position: Clinical Pharmacist CDE
Date: 24-04-2025

☒ 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.

Table 10: Conflict of Interest Declaration for Clinician 10

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai		X		
Abbott		X		
Novo Nordisk		X		
Dexcom		X		
Glaxo		X		
Amgen		X		
Merck		X		
Lilly		X		
Astra Zeneca		X		
HLS Therapeutics		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 11

Name: Dr. Nazli Parast
Position: Clinical Manager, Canadian Women's Heart Health Centre/Prevention & Wellness Centre
Date: 24-04-2025

☒ 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.

Table 11: Conflict of Interest Declaration for Clinician 11

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 12

Name: Shahebina Walji, MD, CCFP, FCFP

Position: MD, CCFP, FCFP, Dip. ABOM; Medical Director Calgary, Weight Management Centre; Assistant Clinical Professor Department of Family Medicine, University of Calgary
Date: 24-04-2025

☒ 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.

Table 12: Conflict of Interest Declaration for Clinician 12

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

References:

1. CADTH (2020) Clinical Evaluation of Interventions for the Management of Insomnia: A Review of Reviews. *CADTH Technology Review* 10
2. Chaput JP, Stranges S (2025) Sleep: The silent hero in cardiometabolic health. *Nutr Metab Cardiovasc Dis* 35 (3): 103782.
3. St-Onge MP, Grandner MA, Brown D, Conroy MB, Jean-Louis G et al. (2016) Sleep Duration and Quality: Impact on Lifestyle Behaviors and Cardiometabolic Health: A Scientific Statement From the American Heart Association. *Circulation* 134 (18): e367-e386.
4. Zhang L, Li G, Bao Y, Liu M (2024) Role of sleep disorders in patients with cardiovascular disease: A systematic review. *Int J Cardiol Cardiovasc Risk Prev* 21 200257.
5. Zheng T (2021) Sleep disturbance in heart failure: A concept analysis. *Nurs Forum* 56 (3): 710-716.
6. Pearson GJ, Thanassoulis G, Anderson TJ, Barry AR, Couture P et al. (2021) 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. *Can J Cardiol* 37 (8): 1129-1150.
7. Columbia GoB (2024). *Diabetes Care*. Available online at: Accessed: April 21, 2025.
8. Canada D (Web Page) Chapter 35: Type 2 Diabetes in Children and Adolescents. Updated Available online at: https://www.diabetes.ca/health-care-providers/clinical-practice-guidelines/chapter-35#panel-tab_FullText. Accessed: April 21, 2025.
9. LeBlanc ES, Smith NX, Nichols GA, Allison MJ, Clarke GN (2018) Insomnia is associated with an increased risk of type 2 diabetes in the clinical setting. *BMJ Open Diabetes Res Care* 6 (1): e000604.
10. Mo C, Wang S, Li X, Li F, Jin C et al. (2024) Benzodiazepine use and incident risk of sudden cardiac arrest in patients with cardiovascular diseases. *Sci Prog* 107 (4): 368504241295325.
11. Kim YH, Kim HB, Kim DH, Kim JY, Shin HY (2018) Use of hypnotics and the risk of or mortality from heart disease: a meta-analysis of observational studies. *Korean J Intern Med* 33 (4): 727-736.
12. Hsu TW, Chen HM, Chen TY, Chu CS, Pan CC (2021) The Association between Use of Benzodiazepine Receptor Agonists and the Risk of Obstructive Sleep Apnea: A Nationwide Population-Based Nested Case-Control Study. *Int J Environ Res Public Health* 18 (18):
13. Meyer EJ, Wittert GA (2024) Approach the Patient With Obstructive Sleep Apnea and Obesity. *J Clin Endocrinol Metab* 109 (3): e1267-e1279.
14. Gao Y, Liu K, Zhu J. Glymphatic system: an emerging therapeutic approach for neurological disorders. Front Mol Neurosci. 2023 Jul 6;16:1138769. doi: 10.3389/fnmol.2023.1138769. PMID: 37485040; PMCID: PMC10359151.
15. Morin CM, Khullar A, Robillard R, Desautels A, Mak MSB et al. (2024) Delphi consensus recommendations for the management of chronic insomnia in Canada. *Sleep Med* 124 598-605.
16. Heikkala E, Jokelainen J, Mikkola I, Auvinen J, Hagnas M (2023) Recurrent prescription of sleep medication among primary care patients with type 2 diabetes: an observational study of real-world registry data. *BMC Prim Care* 24 (1): 90.
17. Chevassus H, Mourand I, Molinier N, Lacarelle B, Brun JF et al. (2004) Assessment of single-dose benzodiazepines on insulin secretion, insulin sensitivity and glucose effectiveness in healthy volunteers: a double-blind, placebo-controlled, randomized cross-over trial [ISRCTN08745124]. *BMC Clin Pharmacol* 4 3.
18. Mikus CR, Oberlin DJ, Libla JL, Taylor AM, Booth FW et al. (2012) Lowering physical activity impairs glycemic control in healthy volunteers. *Med Sci Sports Exerc* 44 (2): 225-231.
19. Nurminen J, Puustinen J, Lahteenmaki R, Vahlberg T, Lyles A et al. (2014) Handgrip strength and balance in older adults following withdrawal from long-term use of temazepam, zopiclone or zolpidem as hypnotics. *BMC Geriatr* 14 121.
20. Gray SL, Penninx BW, Blough DK, Artz MB, Guralnik JM et al. (2003) Benzodiazepine use and physical performance in community-dwelling older women. *J Am Geriatr Soc* 51 (11): 1563-1570.
21. Campbell-Schere D, Walji S, Kemp A, Piccinini-Vallis H, Vallis T (Web Page) Canadian Adult Obesity Clinical Practice Guidelines: Primary Care and Primary Healthcare in Obesity Management. Updated Available online at: https://obesitycanada.ca/guidelines/primarycare Accessed: April 23, 2025.
22. Chaput JP, Janssen I, Sampasa-Kanyinga H, Carney CE, Dang-Vu TT et al. (2023) Economic burden of insomnia symptoms in Canada. *Sleep Health* 9 (2): 185-189.
23. Biddinger KJ, Emdin CA, Haas ME, Wang M, Hindy G et al. (2022) Association of Habitual Alcohol Intake With Risk of Cardiovascular Disease. *JAMA Netw Open* 5 (3): e223849.

24. Karppa M, Yardley J, Pinner K, Filippov G, Zammit G et al. (2020) Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2. *Sleep* 43 (9):
25. Yardley J, Inoue Y, Pinner K, et al. Efficacy and safety of lemborexant in subjects previously treated with placebo for 6 months in a randomized phase 3 study. Sleep Med. 2023;110:111-119. doi:10.1016/j.sleep.2023.07.023
26. Rosenberg R, Murphy P, Zammit G, Mayleben D, Kumar D et al. (2019) Comparison of lemborexant With Placebo and Zolpidem Tartrate Extended Release for the Treatment of Older Adults With Insomnia Disorder: A Phase 3 Randomized Clinical Trial. *JAMA Netw Open* 2 (12): e1918254.

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Patient Input Template

Name of the Drug and Indication	**Lembroxant (Dayvigo®)**
Name of the Patient Group	**Gastrointestinal Society**
Author of the Submission	**Jaymee Maaghop**

1. About Your Patient Group

The GI (Gastrointestinal) Society is committed to improving the lives of people with GI and liver conditions, supporting research, advocating for appropriate patient access to healthcare, and promoting gastrointestinal and liver health.

We are a national charity formed in 2008 on the groundwork of its partner organization, the Canadian Society of Intestinal Research (CSIR), which was founded in Vancouver in 1976. We receive national and international attention, simply because we have earned the respect of both the gastrointestinal medical community and Canadians who battle GI and liver issues daily. Our website, available in English and French, received 9,329,479 pageviews in 2023 and 8,890,977 in 2024.

All our programs and services focus on providing Canadians with trusted, commercial-free, medically-sound information on gut (including obesity) and liver diseases and disorders in both official languages. Our BadGut® lectures, quarterly *Inside Tract*® newsletter, pamphlets, support groups, and educational videos arm Canadians with the information they require to better understand and manage their specific needs. We also work closely with healthcare professionals and governments at all levels toward system-wide improvements in care and treatment.

2. Information Gathering

We completed this submission by using information we obtained from meetings and discussions with healthcare professionals and researchers, as well as questionnaires and interviews from various surveys we conducted on digestive and liver diseases and disorders. We also interviewed an individual living with a digestive condition and a diagnosis of chronic insomnia, who is currently taking Dayvigo® as part of her treatment for insomnia.

In our recent issue of the *Inside Tract*® newsletter, we released an article discussing the Vital Links Between Sleep and GI Conditions. We highly encourage CDEC reviewers to read this article. It is available in both English and French at https://badgut.org/sleep/.

3. Disease Experience

Insomnia can involve sleep problems, such as difficulty falling asleep, staying asleep, or waking up too early and being unable to fall back asleep. If any of these occur at least three times a week for three months or longer, it is considered chronic insomnia. Statistics Canada[1] reports that an estimated 10% to 15% of

Canadians experience symptoms of insomnia that affect their daytime functioning, while 6% to 10% meet the criteria for an insomnia disorder. This means that approximately 2.2 million to 3.7 million Canadians may be facing challenges with a sleep disorder.

Chronic insomnia can have significant impacts to productivity, including both absenteeism and presenteeism, with an estimated price tag of $19.6B annually lost in GDP in Canada.[2] Beyond the workplace, insufficient sleep can affect an individual's emotional well-being, behavior, and interactions, contributing to memory lapses, accidents, injuries, and mood disturbances. These effects can have serious consequences on physical health, mental well-being, and public safety.

Chronic insomnia disorder is an independent condition that is also closely linked to a range of comorbidities, including cardiovascular disease, diabetes, obesity, cancer, and gastrointestinal (GI) diseases and disorders. **The relationship between sleep and digestive health is complex**. Some medications used to treat GI conditions, including obesity, may contribute to insomnia, while poor sleep can worsen or even trigger GI symptoms. The connection is bidirectional, but it is unclear whether lack of sleep exacerbates these conditions or if symptoms are causing the sleep problems. However, successful sleep management can only be achieved by addressing both chronic insomnia and any comorbid GI conditions.

Crohn's disease and ulcerative colitis are both inflammatory bowel diseases (IBDs) that can arise at any age, commonly occurring in young people. IBD is a chronic disease. Diarrhea, rectal bleeding, and abdominal pain are some of the common recurring symptoms of IBD. Inflammation decreases the intestine's absorptive surfaces, triggering watery stools that can lead to fecal urgency and poor control of bowel function. Low red blood cell count (anemia) can result from blood loss due to ulcerations in the intestine and from general malnutrition due to decreased nutrient absorption and the debilitating effects of the disease.

In our 2024 IBD Unmet Needs Survey (https://badgut.org/2024-ibd-survey-results/),[3] many respondents reported sleep interruption, with 56% having difficulty sleeping or insomnia. These are typically due to bowel movements disrupting their sleep, the fear of having sudden bowel movements, and chronic abdominal pain. Even when the disease is inactive, patients continue to report poor sleep, with some resorting to sleeping pills, experiencing decreased daytime energy, increased fatigue, and overall poor sleep quality. Also, poor sleep quality is associated with disease severity, as sleep deprivation can elevate levels of proinflammatory cytokines, which trigger an immune response.

Microscopic colitis (MC) is another form of IBD characterized by sudden, chronic watery diarrhea without blood. On average, diarrhea occurs six to nine times a day, but it can be more than ten. For many individuals, about one-third of these episodes happen at night, severely disrupting sleep and contributing to fatigue.

Irritable bowel syndrome (IBS) is a chronic and often debilitating functional GI disorder characterized by symptoms such as abdominal pain, bloating, and altered bowel behaviours of constipation and/or diarrhea, or alternating between the two. Individuals with IBS often report sleep disturbances. In a study we published on patient experiences with IBS (https://badgut.org/ibs-patient-experience-journal-article/),[4] we found that 20% of those with diarrhea-predominant IBS reported sleep disorders as a comorbidity. Across all three IBS subtypes (constipation-predominant, diarrhea-predominant, mixed), 25-29% of respondents experienced sleep difficulties. People with IBS often face challenges such as longer times to fall asleep, frequent night-time awakenings, and excessive daytime sleepiness.

Obesity is a multi-factorial, chronic, relapsing disease that occurs when a person accumulates an excessive amount of body fat (adipose tissue) that might increase health complications. Persons living with obesity are more likely to report insomnia or trouble sleeping than those who are not. In our 2024 international survey (https://badgut.org/information-centre/a-z-digestive-topics/obesity-journey-survey-report/)[5] about the

perspectives and experiences of individuals living with obesity, with 1,487 respondents, 1,050 of whom completed it, 58% reported having insomnia/difficulty sleeping. Many of our respondents were from Canada (62%). When asked what the most difficult aspects of living with obesity are, several respondents included trouble sleeping/sleep apnea:

- "Activities of daily living difficult washing, dressing socialising exercise sleeping breathing. Going out and having fun with the kids. Trying to lift your mood to do anything."
- "I was diagnosed with sleep apnea about 15 years ago. I know sleep apnea impacts weight and contributes to obesity."

Sleep apnea is a common comorbidity associated with obesity, as excess adipose tissue around the neck can obstruct the airway during sleep, leading to breathing pauses, fragmented sleep, and daytime fatigue. As with other GI conditions, the relationship with sleep disorders is bidirectional. Obesity increases the risk of developing sleep apnea, while sleep apnea can exacerbate weight gain by disrupting hormonal balance, reduced energy levels, and lowering motivation, cognition, and ability for physical activity. After a night of inadequate sleep, the body releases more ghrelin, the hormone that stimulates hunger, and reduces leptin, the hormone that signals fullness. This imbalance can lead to increased calorie intake.

These are just a few of the gastrointestinal conditions associated with insomnia, highlighting the complex relationship between sleep and digestive health. It is crucial to address both insomnia and any comorbid gastrointestinal conditions together to effectively manage symptoms and improve overall well-being.

4. Experiences With Currently Available Treatments

Currently, treatment options for chronic insomnia are limited. Many are either not indicated for long-term use, are challenging to access, or cannot provide truly restorative sleep without next-day drowsiness or impaired daytime functioning.

Cognitive behavioral therapy (CBT) is a proven non-pharmacological treatment, but it can be challenging and costly to access and may not work for everyone. Physicians commonly prescribe medications to treat insomnia, but they are limited in effectiveness and do not meet the needs of patients. These include benzodiazepine receptor agonists (flurazepam, nitrazepam, temazepam, and triazolam), Z-drugs, or non-benzodiazepines (zopiclone, zolpidem), and dual orexin receptor antagonists (suvorexant, lemborexant). However, these are for short-term use only (typically 7-10 days). They also carry increased risks for abuse, misuse, and withdrawal symptoms, and can cause next-day sedation and other side effects. These sedative medications can lead to harmful outcomes such as falls, cognitive deficits, dependency, and even overdose-related mortality.

Physicians may also prescribe off-label antidepressants, anti-psychotics (trazodone, L-tryptophan, and amitriptyline), antihistamines such as diphenhydramine (Benadryl®), and melatonin. Many patients, facing high unmet needs, often resort to other over-the-counter supplements and drugs, such as magnesium, L-theanine, and herbal products (chamomile, lavender, valerian root, etc.), among others. However, these may not be effective and can cause debilitating side effects such as next-day drowsiness, confusion, and constipation.

Given the limitations of these treatments, both patients and physicians recognize the need for more effective and accessible options for managing chronic insomnia.

In 2023, Health Canada approved a new medication, daridorexant (Quviviq®), for the management of adult patients with insomnia. It is a dual orexin receptor antagonist and clinical studies have shown that it is effective at increasing the amount of time adults with insomnia can sleep and improving functioning during the day. There is also no evidence of physical dependence or withdrawal symptoms upon discontinuation. These studies have also looked at people taking this medication for at least 12 months. However, it is currently under review by CDA for a draft recommendation regarding its public reimbursement, so its accessibility through public coverage is still pending.

For individuals suffering from chronic insomnia, effective, long-term treatments are essential and urgently needed. While good quality sleep may seem trivial to some, it is vital for overall health and well-being. With the right therapy, those living with chronic insomnia can find hope and see improvements in their quality of life, ability to function, and mood, allowing them to fully engage in daily activities, free from the persistent challenges of sleep deprivation.

5. Improved Outcomes

There is a significant need for medications to treat chronic insomnia. Patients also need a variety of treatment options so that if one stops being effective, they have other options to rely on.

Unfortunately, many of the current medications for insomnia are only meant for short-term use (7-10 days), and other medications are used off-label. As a result, **patients with chronic insomnia virtually have no effective treatment options**. Individuals suffering from chronic insomnia need better sleep quality and quantity, as well as improved daytime functioning to help them work, study, focus, and enjoy their day-to-day lives. Physicians should screen for comorbid conditions, such as gastrointestinal disorders, when treating insomnia, as these can exacerbate sleep symptoms.

6. Experience With Drug Under Review

We interviewed one individual living with achalasia, a rare disorder, and chronic insomnia. She is taking lembroxant (Dayvigo®) as part of her treatment for insomnia.

For years, she lived with debilitating symptoms of achalasia that went undiagnosed. This included constant vomiting, heartburn, and coughing, with countless nights spent sleeping upright just to have some slight relief from symptoms. What often went unnoticed was the toll this took on her sleep. “Insomnia was something that dawned on me much later as something that I need to care about,” she said. However, long before she received a diagnosis of achalasia, this rare disorder had already disrupted her ability to rest and recover, and sleep deprivation became a defining part of her life.

Diagnosing achalasia can take a long time due to how uncommon the disorder is, and unfortunately, she suffered for decades with misdiagnoses, ineffective treatments, and without proper care. Achalasia occurs when the nerves in the esophagus or the lower esophageal sphincter (LES) become damaged. This damage causes loss of normal esophageal peristalsis and prevents the LES from relaxing properly. As a result, food and liquids may get stuck in the esophagus. Achalasia is a lifelong and progressive disorder, and there is no cure to date.

“Achalasia is throwing up constantly… I never remembered myself without heartburn,” she explained. At one point, she was on the highest dose of anti-nausea medication, but it did not work. Her healthcare team

suspected achalasia when she was sent in for an endoscopy, but by the time it was identified, her esophagus had become flattened from damage.

In 2015, she underwent a temporary operation to open the valve, and now she's waiting for a major surgery, an esophagectomy, to remove the esophagus to connect her throat directly to her stomach. This surgery is done very rarely, and is reserved for those with long-standing untreated achalasia.

However, her insomnia was not treated as a medical issue for years. "No GP ever talked to me about it." Instead, she managed it quietly and on her own for the longest time. When asked about the impact of lack of sleep on her life, she described, "sleep deprivation is a form of torture in war," as the exhaustion crept into every corner of her life.

She spent 20 years sleeping upright to try to control symptoms from gastroesophageal reflux and reduce nighttime attacks. "It takes its toll," she admits. Sudden attacks of reflux interrupted her workdays, and the irritability and daytime drowsiness from chronic lack of sleep affected her relationships with her children, her marriage, and her social life.

Her turning point came when she received a prescription for Dayvigo®. She has been taking it for a year now, at a 5 mg dose, has experienced no side effects, and has noticed a significant improvement in her REM sleep. She said, "I don't think I ever understood what good sleep is and now that I know what it is, no matter what, that is my top priority now. I also don't have anxiety at bed time thinking that I'm going to be up in the middle of the night. Now when I do get up, I can fall back asleep. That is huge for me!"

Before Dayvigo®, she struggled to find relief from her insomnia and tried various over-the-counter remedies, such as melatonin, edible cannabis, Benadryl® and Nyquil®. However, they were ineffective and/or made her feel sluggish in the morning, without providing truly restful sleep. Her experience reflects the broader reality for many individuals struggling with chronic insomnia. Those without effective treatment endure sleepless nights and a diminished quality of life due to inadequate care or limited access to appropriate therapies.

She now sees insomnia not as a secondary concern, but as a health issue that deserves real attention on its own. She also practices sleep hygiene, including avoiding caffeine after mid-day, making her bedroom a haven so that it is a cool temperature and is dark, and minimizes her phone screen time in bed. "Every stage of sleep is so important," she emphasizes. "Diet, physical activity, and sleep should be pillars of health." Sleep is a necessity of living, and with significant improvements in her sleep, she shared, "I can be a better human being, mother, wife, employee. I can show up and function."

7. Companion Diagnostic Test

n/a

8. Anything Else?

n/a

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CDA-AMC may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No.

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 Limited		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.

Name: Jaymee Maaghop
Position: Health Policy and Outreach Manager
Patient Group: Gastrointestinal Society
Date: 2025-04-29

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1 Can't sleep, count sheep. Statistics Canada. Available at: https://www.statcan.gc.ca/o1/en/plus/1653-cant-sleep-count-sheep.
2 Hafner M *et al.* The societal and economic burden of insomnia in adults: An international study. Rand Corporation. 2023. Available at: https://www.rand.org/pubs/research_reports/RRA2166-1.html.
3 Unmet Needs in IBD Survey Report. Gastrointestinal Society. Available at: https://badgut.org/2024-ibd-survey-results/.
4 Attara G. Journal Article: The IBS Patient Experience. Gastrointestinal Society. Available at: https://badgut.org/ibs-patient-experience-journal-article/.
5 Obesity Journey Survey Report. Gastrointestinal Society. Available at: https://badgut.org/information-centre/a-z-digestive-topics/obesity-journey-survey-report/.

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Reimbursement Review

Clinician Group Input

Project Number: **SR0895-000**
Generic Drug Name (Brand Name): lemborexant (DAYVIGO)
Indication: Chronic Insomnia
Name of Clinician Group: Depression and Anxiety Clinician Group
Author of Submission: Drs Serge Lessard, Jeff Habert, Luc Cossette and Roger McIntyre, Manrit Takhar

1. About Your Clinician Group

Our group consists of clinicians who specialize in the treatment of depression and anxiety.

2. Information Gathering

The information was gathered through discussions among the group of clinicians concerned about the lack of access to lemborexant.

3. Current Treatments and Treatment Goals

The current treatment paradigm for chronic insomnia in Canada includes non-pharmacologic (e.g., cognitive behavioural therapy for insomnia [CBT-I]) and pharmacologic (e.g., benzodiazepine receptor agonists, Z-drugs, antihistamines) options. In addition, there are numerous off-label and/or over the counter options, including melatonin, off-label antidepressants, alcohol/cannabis, antihistamines, natural health products, and antipsychotics. However, these alternatives often lack rigorous testing and regulatory oversight, which increases the risk of adverse health effects and side effects, particularly in the absence of robust clinical data supporting their efficacy and safety for patients with chronic insomnia and comorbid depression and anxiety.

The key therapeutic goals for chronic insomnia are to provide effective and long-term relief, allowing patients to experience high-quality sleep. This is particularly relevant for patients with depression or anxiety, given the bi-directional association between sleep quality and mental health. For example, the 2023 Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines target restoring restful sleep as an important objective for the treatment of major depressive disorder.[1]

Recent consensus guidance related to the management of chronic insomnia in Canada noted that most available agents present potential safety concerns or an unclear or hazardous safety and efficacy profile.[2] In clinical practice, antidepressants and hypnotics continue to be widely used to treat patients with comorbid depression and sleep disturbances; however, certain antidepressant classes—such as serotonin-norepinephrine reuptake inhibitors (SNRIs) and monoamine oxidase inhibitors (MAOIs)—can contribute to, or worsen, sleep disruption.[3] Hypnotics are also associated with risk of dependence, tolerance, and a possible link to the onset or exacerbation of depressive symptoms. The ideal treatment would provide effective relief of chronic insomnia, without exacerbating symptoms of depression and anxiety, and ideally contribute to their improvement, while offering benefits that outweigh the risks associated with long-term use.[2] The current alternatives that are reimbursed by the public drug plans do not target the cause of insomnia, and may even contribute to the worsening of depression and anxiety. As a result, patients do not experience good quality sleep, or improvements in their comorbid mental health conditions, which may contribute to impaired daily functioning.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Goals (needs) that are not being met by currently available treatments include:

- Treatments are needed that are appropriate for long-term use
- Treatments are needed that provide effective relief of chronic insomnia (i.e., promote sleep initiation and maintenance, wherein the sleep cycle is reset, and patients are non-sedated upon waking)
- Treatments are needed that promote next-day mental clarity and functioning
- Not all patients (e.g., those with psychiatric comorbidities, respiratory comorbidities [e.g., obstructive sleep apnea], elderly, or patients in acute crises) benefit from available treatments
- Treatments are needed that minimize associated adverse events
- Treatments are needed that minimize the risk of addiction and dependency
- Treatments are needed that minimize drug-drug interaction
- Treatments are needed that are safe when used with other medications

Currently available therapies are limited in their ability to effectively treat chronic insomnia (i.e., unable to restore normal sleep architecture or promote sleep initiation, maintenance, and mental clarity and functioning). Options remain very limited for long-term treatment, with some available therapies potentially worsening insomnia or depression and anxiety symptoms over time or resulting in long-term cognition concerns or patient tolerance necessitating higher doses. Next-day functioning is also negatively impacted by available therapies, with patients experiencing daytime sedation/fatigue, cognitive and psychomotor impairment, reduced engagement in daily activities, and reduced ability to operate motor vehicles. These effects may be further compounded in patients with depression and anxiety, who are often managing additional adverse effects from concurrent psychiatric medications, and are also at an increased risk of mental health decline due to poor sleep.[4] Furthermore, the concomitant use of multiple medications may increase the risk of drug interactions and adverse events, along with reduced adherence due to the complexity of their treatment regimens.[5] This is particularly concerning for individuals with depression, who may be more prone to forgetfulness.[6] Certain treatments can exacerbate or complicate psychiatric disorders, such as reducing motivation or promoting cognitive fatigue (i.e., increasing depressive properties). Additionally, many currently used therapies are used off-label and without clinician prescription/awareness, with limited or poor-quality evidence supporting the efficacy of these agents.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Lemborexant is anticipated to be administered as a first-line pharmaceutical treatment of chronic insomnia (after CBT-I) among patients aged 18 years and older. First-line treatment offers numerous advantages, most notably that patients will be offered lemborexant in place of other therapies associated with a high risk of adverse events or negative impact on mental health comorbidities. Offering first-line lemborexant is consistent with current Canadian consensus guidelines, wherein the limitations of currently available treatments are clearly noted.[2] This recommendation is further supported by the CANMAT guidelines, which identify sleep disorders as a modifiable risk factor for suicide, underscoring the importance of addressing and improving sleep.[1] Lemborexant is preferred by our clinician group (including those working in remote or rural regions) over currently available therapies; however, patient access remains limited by the lack of public reimbursement, with many patients unable to fund lemborexant on their own and clinicians forced to prescribe older molecules. Notably, in a recent survey of 252 Canadian primary care providers, lemborexant was reported as a treatment option that concerned prescribers less commonly than most other sleep medications.[7] This is important, as clinicians often have considerable concerns regarding the safety of benzodiazepines, Z-drugs, and trazodone; however, these options are frequently prescribed due to their accessibility rather than being considered safer or more effective alternatives. Notably, multiple global studies have linked benzodiazepines use to an increased risk of suicide attempts and completions, a finding that is particularly concerning in patients with comorbid depression and anxiety.[8] These concerns further highlight the urgent need for safer, treatment alternatives for insomnia in this vulnerable population.

Lemborexant is particularly well suited for patients with comorbid psychiatric disorders such as depression, mood, or anxiety disorders, as it does not worsen these conditions nor does it produce additional challenges for patients (e.g., weight gain, anticholinergic effects, cognitive dullness). In fact, meta-analysis findings show that improving sleep led to a significant improvement in composite mental health, depression, and anxiety.[4] In general, lemborexant can be used concomitantly with psychiatric drugs (e.g., antidepressants) without any additional safety risks.[9] Given the established bidirectionality between chronic insomnia and disorders such as depression/anxiety, effective treatment for insomnia is essential in improving patients' comorbid conditions. Overall, patients with comorbid psychiatric disorders, as well as other high-risk groups such as the elderly or patients suffering from

trauma, currently face a high unmet need for a safe and effective treatment for chronic insomnia. This unmet need is anticipated to persist in the absence of lemborexant reimbursement. Chronic insomnia increases the risk of dementia, with anxiety and depression also contributing to cognitive decline; hence, treating chronic insomnia in the present can promote improved cognitive functioning in the future.

For any patients already receiving other agents, switching to lemborexant is preferable due to its improved efficacy and side effect profile, although the time required for patients to transition will vary depending on the agent they are currently receiving. Switching to lemborexant will be particularly relevant for patients who report a lack of efficacy, poor tolerability, or impaired next-day functioning with currently available treatments. It may also be beneficial for individuals at risk of dependency, such as with benzodiazepine use, and for those with respiratory concerns, where certain depressants may pose additional safety concerns.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Lemborexant is an appropriate treatment for patients with chronic insomnia aged 18 years and older.. It is the opinion of our clinician group that all patients with insomnia deserve access to this safe and effective treatment option. Reimbursement of lemborexant will allow clinicians to reduce patients' use of sedative drugs that often have very harmful side effects.

Lemborexant is appropriate for use in patients with and without comorbidities and may be particularly suited to patients with comorbid depression and anxiety or a history of trauma due to its favourable effects on next-day functioning and mood,[10] and its lack of residual sedative effects. Owing to its unique mechanism of action, lemborexant is well suited to patients who have failed prior treatment with currently available agents such as Z-drugs or benzodiazepine receptor agonists, as well as patients who have developed a high tolerance to, or are unable to tolerate, these agents. Lemborexant is safe in patients with substance use or alcohol use disorder, as it has a low potential for abuse and does not produce physical dependence. This is particularly relevant given that substance misuse is associated with a 4.5-fold (95% CI: 4.50, 4.58) increased risk of lifetime generalized anxiety and depression.[11]

The effectiveness of lemborexant may be reduced among patients who are refractory or resistant to many prior agents and patients with limited treatment compliance. In instances where patients are receiving relief with currently available agents as a short-term treatment, it may not be necessary to switch patients to lemborexant.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Key outcomes considered in clinical practice are sleep quality (e.g., restful sleep and patient satisfaction), next-day functioning (including alertness first thing in the morning, absence of dizziness upon waking, absence of brain fog, absence of dullness, patients' physical and mental state throughout the day, and their ability to drive), and patients' overall quality of life. The importance of assessing next-day functioning cannot be overstated, with patients' mental clarity having a direct impact on their daily activities, emotional regulation, and ability to work, study, and uphold family responsibilities. This is especially important for shift-workers and caregivers, as well as patients with comorbid depression and anxiety who fear taking a medication that further reduces their productivity/functioning. For patients with major depressive disorder, cognitive deficits may persist even during periods of symptom remission.[12] Therefore, it is essential to have treatment options that do not exacerbate these cognitive effects, ensuring mental clarity and support for optimal daily functioning. Measures of presenteeism and absenteeism can be used to help quantify the potential societal benefits of treatment. Real-world evidence, including family practice surveys on safety and efficacy, may provide useful sources of data. In addition, the daridorexant and lemborexant trials are robust and have meaningful positive outcomes.

Other outcomes of interest include whether patients develop tolerance or dependency and, among patients with comorbid mood and anxiety disorders, the impact of treatment on suicidality or alcohol/substance use disorder. Notably, sleep disorders have been closely linked to suicidal behaviour in patients with depression (odds ratio [OR] 2.45; 95% CI: 1.33, 4.52), underscoring the importance of assessing treatment effects on both sleep and mental health outcomes.[13] The presence/absence of withdrawal symptoms, delirium, and cognitive impairment should also be considered.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Unlike other currently available treatments for insomnia, discontinuing treatment with lemborexant is not anticipated to negatively impact patients' physical or mental wellbeing. In both pivotal trials, no evidence of rebound insomnia was observed, indicating that patients could safely discontinue lemborexant without experiencing withdrawal symptoms or a deterioration in sleep patterns.[14; 15]

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Lemborexant can be administered in inpatient and outpatient settings, including emergency rooms, clinics, hospitals, and at home. Unlike some other currently used treatments, lemborexant has no street value. Lemborexant is easy and safe to prescribe, with no titration needed and minimal risk of side effects, overdose, or dependency.

6. Additional Information

Public reimbursement of lemborexant will enable clinicians to readily provide patients with the most efficacious and well-tolerated available treatment, removing funding restrictions and circumventing the need to prescribe older, less desirable options with a negative safety profile.

There is evidence that when patients with insomnia are treated with Lemborexant, this does not increase the danger to the public. In contrast, individuals' use of benzodiazepines and Z-drugs are known to pose a risk to the public with respect to dangerous driving.

Unfortunately, the importance of treating chronic insomnia can sometimes be overlooked; therefore, our group would like to emphasize that effectively treating this condition is essential for ensuring that patients can be productive members of society across their lifespan. To this end, our clinician group wishes to share our first-hand experiences of the impact that lemborexant has had on our patients:

- *"lemborexant improves sleep significantly, treating the comorbid sleep issue and mental health issue, improving daytime function, with no tolerance addiction or morning sedation."*
- *"It's very rare in psychiatry to hear from patients that you've turned their life around, they feel better about depression and anxiety, and they report doing better in life. However, this is exactly what I'm hearing."*
- *"I have seen improvement in a patient with bipolar II disorder who was struggling with a depressive episode when everything else was failing; she became suicidal as a result and hospitalized. Treating her with lemborexant and seeing immediate results was wonderful and gave her hope again, which was pivotal for stabilizing her."*
- *"I hear that there is no evidence of dependency/abuse – patients like this."*
- *"Patients feel that lemborexant is easy to take, no bad taste; patients can miss a night, and it still works; lemborexant is flexible in dosing and patients are very appreciate of it."*
- *"Patients being very appreciative is a new experience as a clinician. The first patient I prescribed on lemborexant was previously hospitalized due to being suicidal as a result of her insomnia and had already been through everything. She saw the difference with lemborexant even in hospital and then as an outpatient. She was able to return to herself and to her work."*
- *"I treated a patient with major introversions, and nothing was helping, but after treating her insomnia with lemborexant, the patient became better and better and is stable for three years now (anxiety and depression stable and improved)."*
- *"As a clinician, there can be a fear of what to use, so sometimes we don't treat due to fear of what the drug will do. General practitioners can be hesitant to treat insomnia due to unstable comorbidities. For my patients with a combination of anxiety and depression, when lemborexant was introduced, it simplified the approach, with the patient sleeping better and the anxiety and depression presentation being brought to a much better state."*
- *"A patient with sleep issues and OCD had a negative anticipation of going to sleep, and had tried other treatments that didn't work. Now, with lemborexant, for the first time he felt calm going to bed, no longer fearful of nighttime approaching and needing to go to bed. Also helped OCD."*

7. Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

The collective feedback to address these questions was assembled following an advisory board meeting where the topics were introduced. Although the online advisory board meeting was funded by Eisai, this submission of Clinician Input was developed at arms-length from Eisai and the authors had full control over the content.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

EVERSANA medical writers assisted the authors with editing the document and sourcing references. EVERSANA did not provide direction on any content.

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. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Luc Cossette
Position: Head of Psychiatry Services, Alma, Qc
Date: 20-04-2025

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$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				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Jeffrey Habert
Enter: Assistant Professor, University of Toronto, Dept. of Family and Community Medicine
Date: 04-04-2025

☒ 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.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
GSK			x	
Otsuka			x	
Lundbeck			x	
Lilly			x	
BI		x		
Novo Nordisk			x	
Eisai			x	
Idorsia			x	
Pfizer		x		
Amgen			x	
HLS		x		
Elvium			x	
Bayer		x		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Serge Lessard
Position: Assistant Professor, University of Ottawa, Department of Psychiatry
Date: <04-04-2025>

☒ 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.

Table 3: Conflict of Interest Declaration for Clinician 3

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	
Biron			x	
Eisai				X
Elvium			x	
Idorsia				
Lundbeck				x

Otsuka			x	
Takeda			x	
Taro/Sun	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Roger S. McIntyre, M.D., FRCPC
Position: Professor of Psychiatry and Pharmacology, University of Toronto, Canada; Chairman and Executive Director, Brain and Cognition Discovery Foundation (BCDF), Toronto, Canada www.bcdfoundation.ca
Date: 25-04-2025

☒ **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.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Lundbeck			X	
Janssen			X	
Alkermes			X	
Neumora Therapeutics			X	
Boehringer Ingelheim			X	
Sage			X	
Biogen			X	
Mitsubishi Tanabe			X	
Purdue			X	
Pfizer			X	
Otsuka			X	
Takeda			X	
Neurocrine			X	
Neurawell			X	
Sunovion			X	
Bausch Health			X	
Axsome			X	
Novo Nordisk			X	
Sanofi			X	
Kris			X	
Intra-Cellular			X	

NewBridge			X	
Eisai			X	
Viatris			X	
Abbvie			X	
Atai Life Sciences			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Manrit Kaur Takhar
Position: Psychiatrist
Date: 24-04-2025

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Otsuka	X			
Eisai	X			
Janssen	X			
Abbvie	X			
Lundbeck	X			

* Place an X in the appropriate dollar range cells for each company.

References cited

1 Lam RW, Kennedy SH, Adams C, Bahji A, Beaulieu S et al. (2024) Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 Update on Clinical Guidelines for Management of Major Depressive Disorder in Adults: Reseau canadien pour les traitements de l'humeur et de l'anxiete (CANMAT) 2023 : Mise a jour des lignes directrices cliniques pour la prise en charge du trouble depressif majeur chez les adultes. *Can J Psychiatry* 69 (9): 641-687.

2 Morin CM, Khullar A, Robillard R, Desautels A, Mak MSB et al. (2024) Delphi consensus recommendations for the management of chronic insomnia in Canada. *Sleep Med* 124 598-605.

3 Fang H, Tu S, Sheng J, Shao A (2019) Depression in sleep disturbance: A review on a bidirectional relationship, mechanisms and treatment. *J Cell Mol Med* 23 (4): 2324-2332.

4 Scott AJ, Webb TL, Martyn-St James M, Rowse G, Weich S (2021) Improving sleep quality leads to better mental health: A meta-analysis of randomised controlled trials. *Sleep Med Rev* 60 101556.

5 Fornaro M, Caiazza C, De Simone G, Rossano F, de Bartolomeis A (2024) Insomnia and related mental health conditions: Essential neurobiological underpinnings towards reduced polypharmacy utilization rates. *Sleep Med* 113 198-214.

6 Marasine NR, Sankhi S (2021) Factors Associated with Antidepressant Medication Non-adherence. *Turk J Pharm Sci* 18 (2): 242-249.

7 Lessard S, Chow WK, Cook SE, Lessard G, Khullar A (2024) Insomnia Management in Primary Care: Outcomes from a Canadian National Survey Reveal Challenges and Opportunities to Improve Clinical Practice. *Canadian Journal of Medicine* 6 (2): 88-104.
8 Dodds TJ (2017) Prescribed Benzodiazepines and Suicide Risk: A Review of the Literature. *Prim Care Companion CNS Disord* 19 (2):
9 Krystal A, Blier P, Culpepper L, Nierenberg AA, Takaesu Y et al. (2025) Efficacy and safety of lemborexant in subjects with insomnia disorder receiving medications for depression or anxiety symptoms. *Neuropsychopharmacol Rep* 45 (1): e12509.
10 Triantafillou S, Saeb S, Lattie EG, Mohr DC, Kording KP (2019) Relationship Between Sleep Quality and Mood: Ecological Momentary Assessment Study. *JMIR Ment Health* 6 (3): e12613.
11 Virtanen S, Kuja-Halkola R, Mataix-Cols D, Jayaram-Lindstrom N, D'Onofrio BM et al. (2020) Comorbidity of substance misuse with anxiety-related and depressive disorders: a genetically informative population study of 3 million individuals in Sweden. *Psychol Med* 50 (10): 1706-1715.
12 Lam RW, Kennedy SH, McLntyre RS, Khullar A (2014) Cognitive dysfunction in major depressive disorder: effects on psychosocial functioning and implications for treatment. *Can J Psychiatry* 59 (12): 649-654.
13 Wang X, Cheng S, Xu H (2019) Systematic review and meta-analysis of the relationship between sleep disorders and suicidal behaviour in patients with depression. *BMC Psychiatry* 19 (1): 303.
14 Karppa M, Yardley J, Pinner K, Filippov G, Zammit G et al. (2020) Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2. *Sleep* 43 (9):
15 Rosenberg R, Murphy P, Zammit G, Mayleben D, Kumar D et al. (2019) Comparison of lemborexant With Placebo and Zolpidem Tartrate Extended Release for the Treatment of Older Adults With Insomnia Disorder: A Phase 3 Randomized Clinical Trial. *JAMA Netw Open* 2 (12): e1918254.

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Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

Reimbursement Review

Clinician Group Input

Project Number: SR0895-000
Generic Drug Name (Brand Name): Lemborexant (DAYVIGO)
Indication: Chronic Insomnia
Name of Clinician Group: Primary Care Clinician Group
Author of Submission: 24 Family Physicians/Primary Care Practitioners

1. About Your Clinician Group

This is a group of 'grassroots' Family Physicians and other Primary Care Practitioners who have practical, hands-on experience treating insomnia in the community.

2. Information Gathering

Information was gathered through email correspondence with an informal network of Family Physicians across the country.

3. Current Treatments and Treatment Goals

We treat insomnia every day in our practice. We know first-hand the impact on our patients: it affects their mental health, it reduces their work productivity, it leads to an increase in family and parenting dysfunction, it reduces their quality of life. Patients are often desperate.

While we all endorse the important role that CBTi plays in treating insomnia – patients have challenges with access to this treatment. Those fortunate enough to get CBTi will frequently report 'it just isn't enough'. That leads us to medical treatment. Up until now, we have had options – but none are ideal. Although affordable or 'covered', benzodiazepines and 'Z drugs' have challenges with addiction, daytime sedation, important drug interactions and tolerance. None of these are approved for long term treatment of chronic insomnia – which by definition is 'chronic'! Regulators scrutinize our use of these medications and patients are increasingly worried about cognitive issues associated with their use.

Other 'off label' treatments like antidepressants and atypical antipsychotics are frequently prescribed - although these are frequently associated with negative metabolic properties (weight gain), falls and daytime somnolence. Why prescribe them? They are covered.

Enter DORAs and lemborexant specifically. We now have a medication studied and endorsed for long term use, accompanied by an outstanding side effect profile, safe, effective without important drug interactions. While this is natural 'first line' pharmacologic intervention – the most vulnerable patients can often not afford this therapy.

This is the basis for our support.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Current therapies – most of which are 'off label', are not meeting needs for the following reasons:

1. Tolerance and/or addiction – like the benzodiazepines or ‘Z drugs’ (zopiclone, eszopiclone).
2. Daytime somnolence – like trazodone and quetiapine, often used ‘off label’.
3. Risk of falls – trazodone and doxepin, Z drugs and quetiapine.
4. Significant drug interactions – benzodiazepines
5. Negative metabolic side effects (weight gain with atypical antipsychotics, trazodone, mirtazapine)
6. In many patients, lack of efficacy results in escalation of dosing, more side effects and/or patients combining these therapies with cannabis or alcohol.

Finally – while most ‘on label’ drug therapies are indicated for short term insomnia; we find that many of our patients suffer from chronic insomnia. Lemborexant is the only sleep medication with long term safety data.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

For most of us – and what is reflected in the newly published Canadian Consensus on Insomnia - DORAs are first line medical therapy in patients with chronic insomnia.

Considering there are many patients with insomnia who are on mediations with an undesirable side effect and efficacy profile, lemborexant is a suitable medication to replace when switching patients from less desirable therapies.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Virtually all patient groups would be ideal candidates for lemborexant starts – pregnancy and age < 18 for example. Certain patient profiles would especially benefit. These include –

Elderly patients – where risk of side effects, falls and association with dementia makes the ‘traditional’ sleep medications risky. These patients are most like to be impecunious and benefit from a medication which is funded – and safe!

Patients with safety sensitive jobs and shift workers (particularly first responders, professional drivers and medical professionals) where daytime somnolence can have functional impairment which could endanger both the individual but also those in the community.

Patients who are at metabolic risk (obesity, prediabetes, hypertension) for sleep medications that cause weight gain.

In individuals who have sleep apnea and concomitant chronic insomnia, lemborexant is a safe option.

For patients with addiction or abuse tendencies, this medication has a low potential for ‘problem’ use.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Patients in primary care who are initiated on a sleep therapy are assessed regularly. Depending on the intensity and severity of the sleep disorder, patients may be seen for follow up within several weeks. Efficacy is thus established fairly quickly. Treatment response is assessed through taking a sleep history – confirming an improvement in daytime function, absent side effects and restorative sleep.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

While chronic insomnia doesn't 'go away' – there are many circumstances which should trigger the clinician to consider deprescribing. These may include – initiation of other sedating medication (example sedating anti-depressant if this were diagnosed), progressive frailty or patient choice.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Specialists in Family Medicine are well positioned to initiate and monitor therapy. While sleep experts will no doubt view this as an important therapy in their practice – insomnia is exceedingly common and most often treated in Primary Care,

6. Additional Information

This submission is coming from a group of grassroots Family Doctors. We see patients struggle with sleep. We are challenged by having safe and effective options to offer these folk. Lemborexant is an important tool for meeting the needs of these patients.

7. Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   We had help from a medical writer, funded by Eisai, to input our disclosures in the template.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

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. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Richard Ward MD CCFP FCFP
Position: Clinical Associate Professor, Department of Family Medicine, Cummings School of Medicine, University of Calgary
Date: 14/04/2025

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

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			x	
AstraZeneca		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Nazeem Naweed Ahmed
Position: Family MD
Date: 24-04-2025

☒ 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.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eli Lilly	*X*			
Novo Nordisk		*X*		
Aralez	*X*			
Pfizer	*X*			
Teva	*X*			
Astrazeneca	*X*			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Robert Hauptman BMSc, MD, MCFP
Position: Family Physician; Assistant Clinical Professor U of A Department of Family Medicine
Date: 24-04-2025

☒ 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.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

AstraZeneca, GSK, Boehringer Ingelheim, Pfizer, Merck, Abbott, Valeant, Paladin, Bayer, Purdue, Cannimed, Knight, Lupin	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Kevin Saunders MD CCFP
Position: Medical Director Wellness Institute at Seven Oaks General Hospital. Winnipeg, MB
Date: 24-04-2025

☒ 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.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
BMS, Boehringer Ingelheim, Merck, Amgen, Janssen, Eli Lilly, Novo Nordisk, Pfizer				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Albert Anthony Kers
Position: Family Physician
Date: 24-04-2025

☒ 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.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Rachel Soo Jung Han Savoie

Position: Community Family Physician
Date: 24-04-2025

☒ 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.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: John Axler
Position: Member of Scientific Planning committees for The Alliance, Humber RIver Hospital, CME AWay by Sea Courses, Director of Medical Affairs for Centre of Evidence based Medicine
Date: 24-04-2025

☒ 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.

Table 7: Conflict of Interest Declaration for Clinician 7

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 8

Name: Yvonne Kangong
Position: Family Physician
Date: 24-04-2025

☒ 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.

Table 8: Conflict of Interest Declaration for Clinician 8

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

Novo Nordisk, Bausch Health	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 9

Name: Dr. Katherine Savoia
Position: Family Physician
Date: 24-04-2025

☒ 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.

Table 9: Conflict of Interest Declaration for Clinician 9

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 10

Name: Dr. Daniel Ngui, BScPT, MD, FCFP
Position: Clinical Professor, UBC Dept of Family Medicine, Medical Director Fraser Street Medical
Date: 24-04-2025

☒ 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.

Table 10: Conflict of Interest Declaration for Clinician 10

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novo Nordisk		X		
Bayer				X
Astra Zeneca, Valeo, Boehringer Ingelheim, Eli Lilly, Eisai, Idorsia	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 11

Name: Wendy Keller
Position: Nurse Practitioner
Date: 29-04-2025

☒ 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.

Table 11: Conflict of Interest Declaration for Clinician 11

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Astellas	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 12

Name: Dr. Catherine Prendiville
Position: Family Physician
Date: 24-04-2025

☒ 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.

Table 12: Conflict of Interest Declaration for Clinician 12

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 13

Name: Dr Neeraj Bector, MD, CCFP
Position: Family Physician
Date: 24-04-2025

☒ 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.

Table 13: Conflict of Interest Declaration for Clinician 13

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novo Nordisk		X		
Eisai	X			

Pfizer	X			
Prollenium	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 14

Name: Dr. L. Mofford
Position: Family Physician, Community Practice, Calgary
Date: 29-04-2025

☒ 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.

Table 14: Conflict of Interest Declaration for Clinician 14

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Lundbeck/Otsuka	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 15

Name: Dr. Elaine Desnoyers
Position: MD, Owner Lake Louise Medical Clinic
Date: 29-04-2025

☒ 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.

Table 15: Conflict of Interest Declaration for Clinician 15

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 16

Name: Lionel Noronha MD, CCFP, FCFP
Position: Medical Director Stirling Manor; Lead Physician Belleville FHO
Date: 29-04-2025

☒ 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.

Table 16: Conflict of Interest Declaration for Clinician 16

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	X			
Idorsia	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 17

Name: Haleh Peiravi MD, CCFP
Position: Family physician – hospital and community
Date: 29-04-2025

☒ 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.

Table 17: Conflict of Interest Declaration for Clinician 17

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 18

Name: Stephanie Liu
Position: Family physician, Assistant Clinical Professor University of Alberta
Date: 29-04-2025

☒ 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.

Table 18: Conflict of Interest Declaration for Clinician 18

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai				X

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 19

Name: Dr Alan R Egan
Position: GP, Synergy Medical Clinic, Sherwood Park AB
Date: 29-04-2025

☒ 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.

Table 19: Conflict of Interest Declaration for Clinician 19

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 20

Name: J Lynne Gillis
Position: MD - family physician
Date: 29-04-2025

☒ 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.

Table 20: Conflict of Interest Declaration for Clinician 20

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 21

Name: Elaine Desnoyers
Position:
Date: 29-04-2025

☒ 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.

Table 20: Conflict of Interest Declaration for Clinician 20

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 22

Name: Robert Crichton
Position: Family physician working in urgent care in Victoria
Date: 29-04-2025

☒ 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.

Table 22: Conflict of Interest Declaration for Clinician 22

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 23

Name: Dr. Sanjeev Bhatla
Position: Clinical Associate Professor of Family Medicine
Date: 29-04-2025

☒ 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.

Table 23: Conflict of Interest Declaration for Clinician 23

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 24

Name: Karyn Richardson

Position: Family Physician
Date: 29-04-2025

☒ 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.

Table 24: Conflict of Interest Declaration for Clinician 24

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

Reimbursement Review

Clinician Group Input

Project Number: **SR0895-000**
Generic Drug Name (Brand Name): DAYVIGO (lemborexant)
Indication: Chronic Insomnia
Name of Clinician Group: Women's Health Clinician Group
Author of Submission: Claudio Soares, Effie Fanaras, Robert Cohen, Michael Greenberg

1. About Your Clinician Group

Our clinician group consists of physicians who specialize in Women's Health.

2. Information Gathering

Our group met to discuss the impact of lemborexant on patient outcomes in the management of insomnia and how this compares to pharmacological treatments currently available for insomnia.

3. Current Treatments and Treatment Goals

Chronic insomnia (i.e., persistent for 3 months or greater) leads to disability, cognitive and functional impairment, absenteeism, and impacts overall patient health. Insomnia has behavioural and physiological components; as such, management strategies should incorporate treatments that address both these elements. Cognitive behavioural therapy for insomnia (CBTi) is used to address the underlying or contributing behaviors, including screen usage before bed and other sleep maladaptive habits. Pharmacological interventions currently used for patients with chronic insomnia include benzodiazepines and Z-drugs, and off-label medications such as antidepressants and antipsychotics. Patients also self-medicate with over-the-counter products, alcohol, and/or cannabis. Notably, all these pharmacological therapies do not directly target the underlying mechanisms of insomnia but rather provide sedation as a side effect.

Ideally, patients should have concurrent access to CBTi and to pharmacological interventions that directly address the underlying mechanisms of sleep disturbance. Treatment plans should be personalized to consider patient age, physical and psychological comorbidities, and lifestyle. Further, there is significant stigma and misinformation around the need for, and safety of, pharmacological interventions to manage chronic insomnia. This needs to be addressed, as medications can be instrumental to initially addressing the disorder while patients work through the behavioural components of insomnia to achieve lasting remission. Pharmacological therapies should be well tolerated, with few side effects and effective for most patients, irrespective of comorbidities and age, without the risk for dependency and/or addiction.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Most currently available pharmacological therapies for insomnia (e.g., benzodiazepines, Z-drugs, anti-psychotic medications) carry a high risk of dependence and may not be appropriate for patients with comorbid conditions. Patients often report a need for dose-escalation with currently available medications due to dependency and the development of tolerance to its effects – as a result, they often use higher than recommended dosages and for longer periods of time than is recommended according to the product label.

Some of the current medications for insomnia also carry a higher risk for addiction, which may prevent physicians from prescribing medications even for those patients with a great need for pharmacological options to manage chronic insomnia. Available pharmacotherapies do not treat the underlying causes of chronic insomnia and are associated with a range of adverse events (AEs), including prolonged sedation (i.e., hangover effect) and impairing daytime function. Benzodiazepines are associated with increased risk of falls and are therefore not appropriate for older patients who have an inherent greater risk for these events. Drugs with weight gain as a side-effect may be particularly challenging for women, as this can contribute to worsening of conditions such as obstructive sleep apnea (OSA) and is stigmatized (i.e., many patients are unwilling to use medications that may result in weight gain, even if it would relieve chronic insomnia).

The sleep patterns vary among patients, and arousal thresholds change through aging; among women, these changes are influenced by hormone changes as they progress through perimenopause, menopause, and post-menopause. As women enter perimenopause, for example, the arousal threshold for wakefulness drops due to physiological changes, necessitating therapies that allow patients to remain asleep without many awakenings or disruptions that negatively impact daytime function.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Lemborexant should be used as the frontline therapy for chronic insomnia and can be paired with CBTi to address both the behavioural and physiological mechanisms of this condition. Lemborexant's ability to block orexin activity sets it apart from traditional sedatives, offering a different approach to treating chronic insomnia. This unique mechanism minimizes side effects commonly associated with other sleep medications, such as residual sedation and cognitive impairment, enhancing overall patient safety. Lemborexant prevents wakefulness, making it beneficial for patients who struggle to fall asleep or remain sleep. This includes menopausal and post-menopausal women who experience fragmented sleep because of wide fluctuations or changes in hormone levels, and often struggle to stay asleep. It can also be adopted by patients who, until now, had to rely on existing pharmacotherapies for insomnia that produce many side effects and carry a high risk for dependency – these patients could be successfully cross-tapered to lemborexant.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Most patients with chronic insomnia would benefit from lemborexant, including those who may not be eligible for current pharmacological therapies, such as those with comorbidities (e.g., irritable bowel syndrome, fibromyalgia, migraines, OSA, anxiety, depression, patients on multiple medications that could pose challenges due to drug-drug interactions, or patients with advanced age). Patients in caregiver roles need therapies that do not result in a hangover effect or cognitive impairment; lemborexant fulfills this role by allowing patients to wake as needed. Perimenopausal, menopausal, and post-menopausal women suffering from insomnia could all benefit from lemborexant, and it could be used in combination with hormone therapy to address the sleep disturbances associated with changes in reproductive stage. Many perimenopausal women start experiencing sleep disturbances prior to the development of vasomotor symptoms (hot flashes, night sweats) and early use of lemborexant could help to minimize the negative impact of changing sleep patterns on wellbeing and overall functioning. Lemborexant would also be an appropriate choice for patients who report sleep disturbances due to shift work.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Insomnia is characterized not only by the challenges in falling asleep and staying asleep, but also by the impact of poor/disrupted sleep on daytime function. As such, for a treatment of insomnia to be clinically meaningful, it is important to show effective and safe changes in sleep patterns and a positive effect on daytime functioning (e.g., no lingering drowsiness or sedation the next day). Lemborexant has shown to be effective in both domains, with good safety and tolerability profiles.

Clinically meaningful response is individualized to the patient's needs. Reported improvements include the following:

- Improved time to sleep onset

- improved sleep consolidation

- faster return to sleep if wake in the night

- more restored in the morning without hangover

- elimination of need to nap

- improved cognitive function - specifically improved concentration, short term memory, and executive function

- improved mood symptoms - less depression and anxiety

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Insomnia is a multidisciplinary disorder that may include input from family physicians and specialists such as gynecologists, neurologists, psychiatrists, and cardiometabolic specialists.

6. Additional Information

In addition to the clinical impairment associated with chronic insomnia (i.e., such as disability, functional and cognitive impairment), this condition has a substantial impact on patient quality of life and functioning, with societal/economic costs, including those related to increased incidence of falls/accidents, absenteeism, and self-medication leading to addiction.

Clinicians emphasize that chronic insomnia negatively impacts overall health in women and has been associated with increased risk of mental health disorders, cardiometabolic conditions, and alcohol use. Use of lemborexant could be important to improve the overall wellbeing of women, potentially minimizing long-term healthcare resource utilization and associated costs. Medications with a potentially more affordable upfront costs (e.g., benzodiazepines, Z-drugs) are in fact associated with safety concerns that manifest with greater long-term costs.

7. Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   Yes. Our group had the support of a medical writer that documented our opinions and collated them into the template. The medical writer was funded by Eisai Canada.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   Yes, as above.

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. **Please note that this is required for <u>each clinician</u> who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Claudio N Soares MD, PhD, FRCPC, MBA
Position: Professor of Psychiatry, Queen's University. President, the Menopause Society.
Date: 23-04-2025

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Bayer, Otsuka, Eisai			X	
Astellas, AbCellera, Idorsia, Diamond Therapeutics		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Effie Fanaras
Position: Respirology and Sleep Medicine; Medical Director, Medsleep
Date: 24-04-2025

☒ 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.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Robert Cohen MD, CCFP, Somnologist (ESRS)
Position: Sleep Physician at the Centre for Sleep and Human Performance, Calgary, Alberta
Date: 23-04-2025

☒ 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.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Eisai			X	
Idorsia			X	

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Michael Greenberg MD
Position: Physician at McGill Executive Institute and private practice
Date: 28-04-2025

☒ 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.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Referernces cited

[1]Lessard S, Chow WK, Cook SE, Lessard G, Khullar A (2024) Insomnia Management in Primary Care: Outcomes from a Canadian National Survey Reveal Challenges and Opportunities to Improve Clinical Practice. *Canadian Journal of Medicine* 6 (2): 88-104.
[2]Ardeljan AD, Hurezeanu R (2025). *Lemborexant*. eds). StatPearls Publishing: Treasure Island (FL).