CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

daridorexant (Quviviq)

(Idorsia Pharmaceuticals Canada Ltd.)

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

December 20, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH 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.

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

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

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Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: daridorexant (Quviviq®)
Indication: chronic insomnia disorder
Name of Patient Group: Gastrointestinal Society
Author of 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, including obesity.

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 these issues daily. Our website, available in English and French, received 9,329,479 pageviews in 2023.

All our programs and services focus on providing Canadians with trusted, commercial-free, medically-sound information on a wide variety of topics related to obesity, gut, 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.

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, and many are either not indicated for long-term use or are challenging to access. Cognitive behavioral therapy (CBT) is a proven non-pharmacological treatment, but it can be challenging and costly to access and may not be effective for everyone. Physicians commonly prescribe medications to treat insomnia, but they also 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 may also lead to harmful outcomes such as falls, cognitive deficits, dependency, and even overdose-related mortality. Physicians may also prescribe off-label antidepressants and anti-psychotics (trazodone, L-tryptophan, and amitriptyline).

Due to high unmet needs, some patients also resort to taking over-the-counter supplements and drugs. These include melatonin, magnesium, L-theanine, herbal products (chamomile, lavender, valerian root, etc.), and antihistamines (diphenhydramine), among others. However, they may not be effective and can cause debilitating side effects such as next-day drowsiness, confusion, and constipation.

Given the limitations of these treatments, there is a need for more effective, accessible options for managing chronic insomnia.

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.

It is crucial to highlight that 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

Daridorexant (Quviviq®) is a dual orexin receptor antagonist. While we have not interviewed patients who have used this medication, clinical studies in the Health Canada product monograph 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.

For individuals suffering from chronic insomnia, an effective, long-term treatment such as Quviviq® can truly be life-changing. 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, leading to the ability to fully participate in daily activities, free from the persistent challenges of sleep deprivation.

7. Companion Diagnostic Test

n/a

8. Anything Else?

No.

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.

   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 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
n/a				

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 & Outreach Manager
Patient Group: Gastrointestinal Society
Date: **2024-12-19**

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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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CADTH Reimbursement Review

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Quviviq/daridorexant
Indication: Insomnia
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.

Migraine Canada is a federally registered national charity that was founded in late 2018 with the mission of providing support, education, and raising awareness about the impact of migraines. We are dedicated to advocating for optimal care for those living with migraines and supporting research efforts to find a cure. With the help of dedicated physicians and contributors, Migraine Canada delivers evidence-based, up-to-date disease and treatment information to Canadians who are affected by migraines, including patients, caregivers, and healthcare professionals. Through various channels such as our website, social media platforms, and forums, Migraine Canada actively works to increase awareness and education. We achieve this by creating and sharing up-to-date electronic and print materials that provide essential information about migraines to patients, caregivers, and healthcare professionals alike. We have a growing community

of over 6,000 individuals subscribing to our email list. Additionally, we provide patient support through participation in regional online support groups, with close to 7,500 following our social media channels.

Migraine Canada's Head Office is located at 20 Loftus Road, Phelpston, ON L0L 2K0. A total of 3 part- time staff are responsible for the operations of Migraine Canada. Its main website is www.migrainecanada.org.

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 and Migraine Canada used a variety of methods, including sleep survey research by both organizations, individual interviews with people who have insomnia and have tried/take other treatments, individual interviews with people who have tried Quviviq. Migraine Canada launched a survey on insomnia and migraine, in October 2024. The data gathered from these sources highlights the urgent unmet needs in the treatment of chronic insomnia and supports the case for the reimbursement of Quviviq.

1. Sleep Survey Research

To support this submission, 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 extra 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 sleep/insomnia (and their level of sleep expertise), and determine the application and perceived efficacy of different sleep remedies and treatments.

Insomnia is 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 of respondents say 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) Eight patients who have struggled with chronic insomnia and have attempted a range of therapies and treatments were interviewed one-on-one by MDSC to obtain information for this submission – one person had direct experience taking Quviviq, and one person had experience with the DORA class, but not Quviviq. For additional information, we also spoke with several family members.
b) We also had lengthy conversations with two clinicians - a family doctor and a psychiatrist.
c) 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.
d) Data and comments from a 2024 survey of patients with insomnia and migraine were also reviewed (prepared by Migraine Canada).

Also included as mentioned above is information collected through an on-line survey Migraine Canada launched in October 2024 to solicit input from the community. Additional data included in this submission was drawn from a Quality-of-Life online survey that was launched by Migraine Canada in late fall of 2021. Both surveys were promoted across Canada through Migraine Canada's digital and social media channels.

The recent survey had a total of 177 respondents who live with migraine and experience sleep issues/insomnia. In total, 1,165 Canadian adults with migraine and their caregivers responded to the Quality-of-Life survey from 2021.

The national survey launched this fall (2024) to gather additional insights to support our submission and seek input from patients with experience on Quviviq. It was 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 15 respondents who have experience with the DORA class, including 1 person with Quviviq experience.

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

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

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 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 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%2

0patients%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.

One individual we spoke to described, "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 Complex Relationship Between Insomnia and Migraine

Similar to mental illness, insomnia is a common complication individuals living with migraine also experience, in addition to mental health issues like depression and anxiety. Research suggests that the relationship is complex between migraine and insomnia with 50% reporting that poor sleep is a trigger. https://pubmed.ncbi.nlm.nih.gov/15985108/

In Migraine Canada's Quality of Survey (1165 participants), issues with sleep is significant ranging from only 7% having no issues with sleep to 38% always or regularly having sleep disrupted due to their migraine. In the survey launched fall 2024, similar results were realized, with over 50% (50.7%)experiencing poor sleep frequently. They reported experiencing poor sleep three or more times per week. 42.96% experience poor sleep every night. Only 1% claimed to experience sleep issues rarely or never.

Sleep disruption reported by patients caused by migraine over the past month was significant for respondents. Close to 20% reported 16-30 days as always or very often disrupted, followed by 19% who reported 11-15 days of disrupted sleep.

Patients rated their quality of sleep as very poor (17%), often disrupted (37%) and sometimes disrupted (30%). Only 16% rated their sleep as "good". When as specifically if migraine impacts sleep, 84% of patients attribute their migraine as having a negative impact.

When asked how often patients experience poor sleep, close to 28% reported sleep issues nightly and close to 41% experience issues 3 or more nights each week.

Over 90% of patients have had these symptoms lasting more than 3 months. Close 20% have been diagnosed with insomnia by a healthcare provider. Close to 60% have informed/spoken with a healthcare professional about their sleep issues.

The Widespread Impacts of Poor Sleep

Insomnia disrupts nearly every aspect of life, from personal relationships to professional responsibilities. 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".

- 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.
- The results from Migraine Canada's QofL survey, asked respondents to what extent sleep problems interfere with daily functioning (ie 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 results from Migraine Canada's fall survey had similar results on how insomnia has had a notable negative impact on various aspects of the daily lives. 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 over 34% of the respondents who reported regular or constant difficulty in this area.
- Additional areas reported in Migraine Canada's fall 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.
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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 only 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."

Ripple Effects on Families and Caregivers

The condition doesn't just affect individuals—it ripples outward to impact families and caregivers. Partners and family members often endure sleepless nights alongside their loved ones, leading to stress, frustration, and relationship strain. Parents may find their ability to care for children diminished, while spouses often take on additional household responsibilities. Social connections can weaken 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."

A caregiver noted of the daughter with insomnia that she cared for: *"At best she would have a few hours of sleep a night, but it was never a good sleep."*

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 the 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."

An Urgent Need for Better Treatments

Current treatments for chronic insomnia fall short of addressing its multifaceted impact. Many available options come with undesirable side effects or risks of dependency, leaving patients to rely on off-label medications or self-medicate with substances that can worsen their health. There is a clear and urgent demand for innovative therapies that not only alleviate symptoms but also improve patients' overall well-being without causing additional harm.

Developing effective and safe solutions for chronic insomnia could transform the lives of those affected, providing relief for patients, their families, and society as a whole. This is a critical opportunity to bridge a glaring gap in care and address the profound needs of millions living with this debilitating condition.

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

"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 grump when I haven't slept. And, if I have something important the next day the stress of not sleeping is High."

"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

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).

Pathways to Treatment

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.

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.

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."

Limitations of Current Prescription Treatments

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. Medications like benzodiazepines and non-benzodiazepine hypnotics (Z-drugs) may help some individuals fall asleep but are far from ideal. Patients often report side effects such as next-day drowsiness, cognitive impairment, rebound insomnia, and dependency. The risk of developing tolerance to these medications frequently leads to prolonged use, even when patients are dissatisfied with their effectiveness. Many described the process of discontinuing these medications as more distressing than the insomnia itself, further entrenching the cycle of dependency.

- 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.

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 is the sedative hangover many experience, leaving them feeling groggy, sluggish, and unproductive the following day.

Exploration of Alternative Therapies
In their pursuit of relief, many patients turn to a range of non-prescription interventions, including cognitive-behavioral therapy for insomnia (CBT-I), mindfulness exercises, relaxation techniques, and rehabilitation programs. While some find these approaches beneficial, they are often limited by accessibility challenges, with public psychological support difficult to obtain without significant out-of-pocket expenses. For others, these methods are only partially effective or fail to provide sustained relief. Even procedures like sleep studies, while helpful for diagnosing issues, rarely lead to immediate solutions and involve long waiting periods.

In MDSC's survey:

- One-half of respondents (50%) used 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.).

CBTi: MDSC's sleep and mental health survey asked respondents specifically about the effectiveness of CBTi. As noted above, few had tried CBTi (7%).

Regarding CBT, 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." And, "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. While such approaches may initially appear to alleviate symptoms, they often exacerbate the problem. For example, alcohol may help individuals fall asleep but disrupts the sleep cycle, leading to frequent awakenings, poor sleep quality, and diminished REM sleep. Similarly, chronic cannabis use can result in tolerance, dependency, and withdrawal symptoms, further complicating sleep and overall health. These behaviors not only fail to resolve the underlying condition 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.

- In Migraine Canada's survey, 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%).

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

"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".

The Need for a Paradigm Shift
Existing insomnia treatments clearly fail to meet the needs of patients, underscoring the urgency of advancing therapeutic options. A significant concern with current therapies is the lingering drowsiness and impaired functioning that many patients experience the day after taking these medications. These side effects not only reduce quality of life but also undermine the effectiveness of treatment. Innovative solutions, including medications with novel mechanisms of action, are desperately needed to provide safe, effective, and comprehensive management of this debilitating condition.

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?

Minimizing Side Effects for Sustainable Use
Patients with chronic insomnia have emphasized 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. 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.

One patient MDSC interviewed said, "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."

Another patient said, "Knowing that after taking a sleeping pill, sleep is a sure thing, I'd be happy to navigate some initial grogginess upon waking."

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, patients consistently voiced the need for better daytime outcomes—feeling rested, alert, and ready to participate fully in their daily lives. Current medications often leave individuals groggy or fatigued, compromising their ability to work, think clearly, and engage in their routines. Patients 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. 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 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.

As a mental illness and a chronic neurological disease like migraine, patients with chronic insomnia 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. In the Quality of Life survey Migraine Canada conducted, close to 17% of respondents were on disability. This reality underscores the necessity of including innovative insomnia treatments like Quviviq in public drug plans to ensure no one is left without support due to financial constraints. Anything less represents a barrier to equitable care, undermining the well-being of affected individuals and the broader public health framework.

One caregiver to a daughter taking Quviviq that MDSC spoke with noted that they access all medications for the daughter (both parents are retired and without private plans) via a provincial disability program (Assured Income for the Severely Handicapped, or AISH). In order for a drug to be reimbursed via AISH it must be listed on the provincial formulary.

Hope for a Novel Treatment Approach

The prospect of a new medication that operates through a novel mechanism of action has ignited a sense of hope among patients and caregivers. The individuals MDSC interviewed expressed optimism that such a treatment could address insomnia without the debilitating side effects associated with older medications. 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.

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. 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".

"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.

MDSC and Migraine Canada employed several avenues to find patients in Canada that have tired Quviviq, including reaching out to clinical trialists; outreach via our networks, volunteers and partners; including the recent survey launched this fall. MDSC interviewed 1 person who was the caregiver to a daughter taking Quviviq – the parents/caregivers were both retired, and the daughter was between 18-30 years old, non-verbal due to living with Cerebral Palsy. In Migraine Canada's survey there was 1 person who reported having experience with Quviviq, and 15 patients overall that had experience with the DORA class.

Unique Benefits of Quviviq: From an efficacy standpoint, the caregiver noted their daughter started sleeping better immediately after starting Quviviq. The caregiver noted that for the first time in the daughter's life, the daughter slept 8 hours straight through the night – and some nights she was even able to sleep 10 hours. The caregiver described her reaction to her daughter's sleeping:

"My jaw dropped; I couldn't believe it. The benefits happened so quickly. In addition to sleeping through the night, I could see that in the morning her eyes were brighter; you could visibly see the different in her face, and her anxiety dropped. If it's possible, because she's normally just a happy-go-lucky child despite her illness, she was happier and calmer – and it was a different happy. It was more of a clam happy vs. a manic happy."

The same caregiver noted that they had never tried prescription medications for their daughter's insomnia before because they knew they were sedating, and they didn't want to sedate her. But when they learned Quviviq was not associated with sedation, they were excited to try it. And they are so pleased that they did try it. The caregiver expressed the positive improvement in their daughter's sleep as:

"This is a huge change. It is a night and day difference. [With Quviviq] she she's calmer and she sleeps longer overall."

With respect to side effects, the caregiver expressed that there were none that they noticed outwardly (as the daughter is non-verbal). “I didn’t detect any side effect. I didn’t notice her being off balance or drowsy the next day or anything”. The parents noted that because of the daughter’s Cerebral Palsy they were previously concerned about anything that would make her unsteady on her feet, and she’s already quite unsteady when she walks, so they’re pleased that there has been no impact on her steadiness/ability to walk.

They also expressed that taking Quviviq away from the daughter now would be devastating:

“It’s improved her quality of sleep so incredibly that now her anxiety is also lowered. And, to take that away from her would be devastating – to reverse an improvement like that, especially for someone without language skills, is devastating.”

To access Quviviq so far the parents have been using free samples from their physician. However, normally they would access her medications via AISH. They have appealed 3 times to AISH with no luck. Again, AISH noted that the drug must be on the common drug list in order to be covered. They have a 100 day supply of the medication and they don’t know what the will do if it isn’t available via AISH after that as they can’t afford to pay for Quviviq.

The caregiver not only noted that Quviviq started to improve her daughter’s sleep right away, but on a daily basis the medication takes effect as described on the label – it takes only 30 minutes for the daughter to fall asleep: “We would put her in bed and read to her for 30 minutes as that’s how long it says it takes for the drug to work, and she would fall asleep in that 30 minutes.

As far as expectations for Quiviq, the caregiver noted that they don’t expect the drug to help their daughter sleep 8 hours every night, “because what human does that”.

With respect to the impact that Quviviq is having on the parents, they expressed it as positive as well. “We get more sleep too, because our daughter is sleeping, and we don’t have to struggle with her anxiety, because that’s calmed as well.”

- Specifically in the Migraine Canada survey, 60% of patients had some or significant improvement in their sleep/insomnia on a DORA compared to any previous treatments they have used.
- In the same survey, 47% of patients reported no side effects on a DORA, while 20% reported having some side effects, which were listed as nightmares. Fifty percent of these respondents said the medication was tolerable and they continued to take it; while 14% said they needed to stop taking the medication, including one respondent who said they could not afford to pay for the medication.
- According to Migraine Canada’s survey, to access the medication, 7% reported receiving a sample from a healthcare provider, 66% reported having accessed it with private coverage, and 20% paid out-of-pocket.

The DORA class of medications has not been associated with dependency and habituation given their mechanism of action is different then benzo/Z-drug classes. This is a critical factor for patients who are wary of becoming reliant on medication. The promise of effective sleep relief without the burden of addiction is a compelling reason why Quviviq should be made widely accessible.

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.

Not applicable

8. Anything Else?

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

Chronic insomnia remains a pervasive and debilitating condition with limited effective treatment options. The primary challenge lies in the absence of safe, long-term solutions that address both the symptoms and underlying causes of insomnia without significant side effects or dependency risks. Although medications like benzodiazepines and Z-drugs can help some patients initiate sleep, their long-term use is often accompanied by tolerance, dependency, and cognitive impairments, leaving patients with few sustainable options.

Behavioral therapies, such as cognitive-behavioral therapy for insomnia (CBT-I), are recognized as highly effective interventions. However, accessibility remains a significant barrier due to a shortage of trained professionals, lengthy waitlists, and out-of-pocket costs, which make these therapies unattainable for many. As a result, patients with chronic insomnia are left with an unmet demand for innovative treatments that balance efficacy, safety, and long-term usability.

Addressing Inequities in Access to Care
A glaring issue in insomnia 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
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 U.S. economy, for example, incurs an estimated $44.6 billion in annual productivity losses from absenteeism linked to poor sleep. These costs are further compounded by additional healthcare expenses, such as emergency department visits, management of exacerbated comorbidities, and repeated consultations with healthcare providers.

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.

The introduction of novel medications with unique mechanisms of action, such as Quviviq, offers a promising solution for patients who have been underserved by existing options.

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 jointly by the staff at Mood Disorders Society of Canada and 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 independently created the on-line Quality of Life survey (2021) and the Sleep survey (2024). Analysis of both surveys was completed internally. MDSC worked with Narrative Research on its mental health and sleep survey.

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 – Mood Disorders Society of Canada & Migraine Canada

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
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: Dave Gallson
Position: National Executive Director
Patient Group: Mood Disorders Society of Canada
Date: December 20, 2024

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
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: National Executive Director
Patient Group: Migraine Canada
Date: December 20, 2024

SLEEP & INSOMNIA

Menopause Chicks.com

December 20, 2024

SHIRLEY WEIR

INSOMNIA & MENOPAUSE

This is our 2nd Sleep Survey (first in 2021) and overall themes have remained the same or increased. Women aged 45-64 continue to feel sleep disruption and insomnia should be magically addressed without medical intervention and their medical providers continue to endorse this via lack of approved treatment information & education.

SHIRLEY WEIR

Founder, Menopause Chicks

- Majority of respondents 45-64 years old
- 28% experience poor sleep daily; 43.5% experience poor sleep 3 or more times per week; 18.5% 1-2 times per week = for a whopping 90%
- Difficulty staying asleep is most common
- 85% blame hormone changes
- **Poor sleep significantly impacts: energy levels, ability to exercise, mood & cognition**
- Majority (60%) believe they should be able to manage their sleep on their own
- 39% have tried over the counter treatments
- 54% tried anti-allergy medication ie. Claritin (!)
- 72% have discussed with their doctor (70% have a family doctor!; 27% have a Naturopathic Doctor, 23% have a specialist on their health team)
- 30% have tried prescription treatment (Response for Hormone Therapy: 44%);
- **Majority of sleep aid/prescriptions are SSRIs**
- 7% have tried CBT-i
- **Majority not yet/not at all satisfied with current management of insomnia**

60%

believe sleep issues “should” be addressed on their own

43%

meet definition of insomnia

Majority

not yet satisfied with current management of insomnia

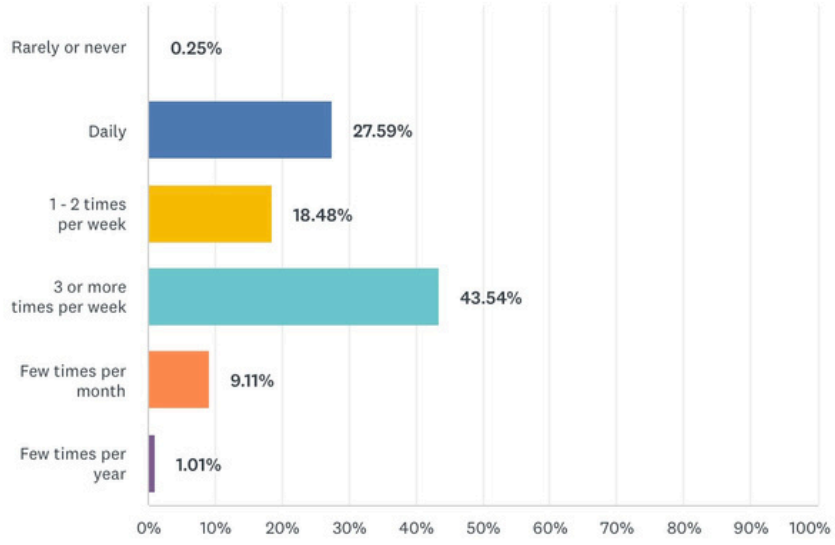
Page 1: Thank you for taking a few minutes to help shape the future of women's sleep health.

Q1

Customize Save as

Do you ever experience poor sleep?

Answered: 395 Skipped: 9



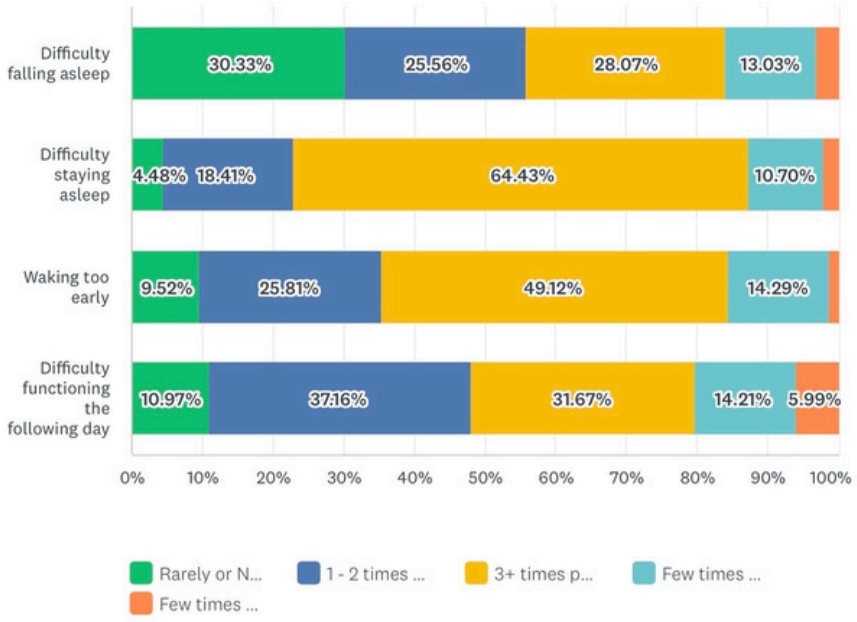
ANSWER CHOICES	RESPONSES	
Rarely or never	0.25%	1
Daily	27.59%	109
1 - 2 times per week	18.48%	73
3 or more times per week	43.54%	172
Few times per month	9.11%	36
Few times per year	1.01%	4
TOTAL		395

Q2

Customize Save as

Insomnia is defined as: difficulty falling asleep, difficulty staying asleep, waking too early or difficulty functioning the following day. How often is your sleep impacted by:

Answered: 403 Skipped: 1



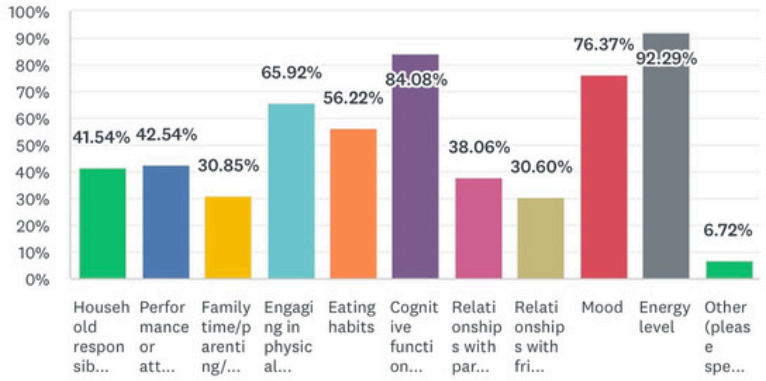
	RARELY OR NEVER	1 - 2 TIMES PER WEEK	3+ TIMES PER WEEK	FEW TIMES A MONTH	FEW TIMES A YEAR	TOTAL
Difficulty falling asleep	30.33% 121	25.56% 102	28.07% 112	13.03% 52	3.01% 12	399
Difficulty staying asleep	4.48% 18	18.41% 74	64.43% 259	10.70% 43	1.99% 8	402
Waking too early	9.52% 38	25.81% 103	49.12% 196	14.29% 57	1.25% 5	399
Difficulty functioning the following day	10.97% 44	37.16% 149	31.67% 127	14.21% 57	5.99% 24	401

Q3

Customize Save as

How has insomnia negatively impacted your day to day life?

Answered: 402 Skipped: 2



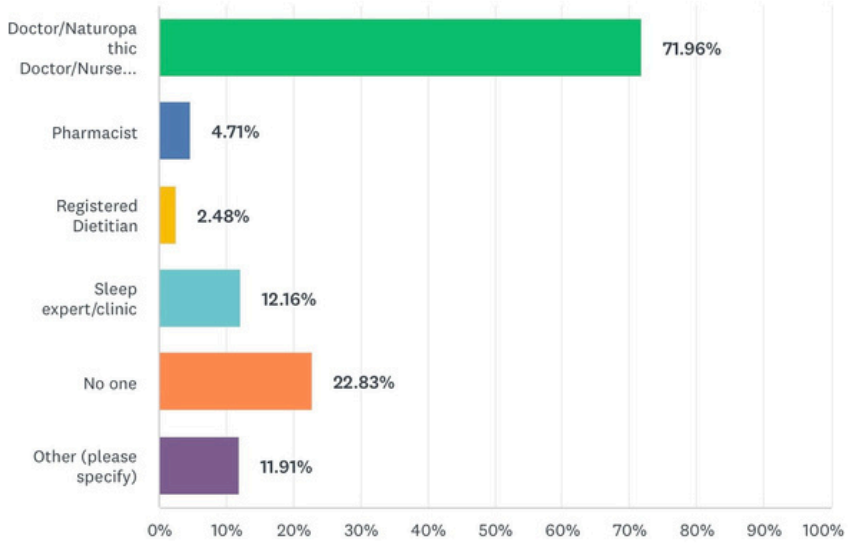
ANSWER CHOICES		RESPONSES	
Household responsibilities		41.54%	167
Performance or attendance at work		42.54%	171
Family time/parenting/caregiving		30.85%	124
Engaging in physical exercise		65.92%	265
Eating habits		56.22%	226
Cognitive function (focus, attention, memory)		84.08%	338
Relationships with partner		38.06%	153
Relationships with friends/social interactions		30.60%	123
Mood		76.37%	307
Energy level		92.29%	371
Other (please specify)	Responses	6.72%	27
Total Respondents: 402			

Q4

Customize Save as

Who have you spoken to about your insomnia/sleep health?

Answered: 403 Skipped: 1



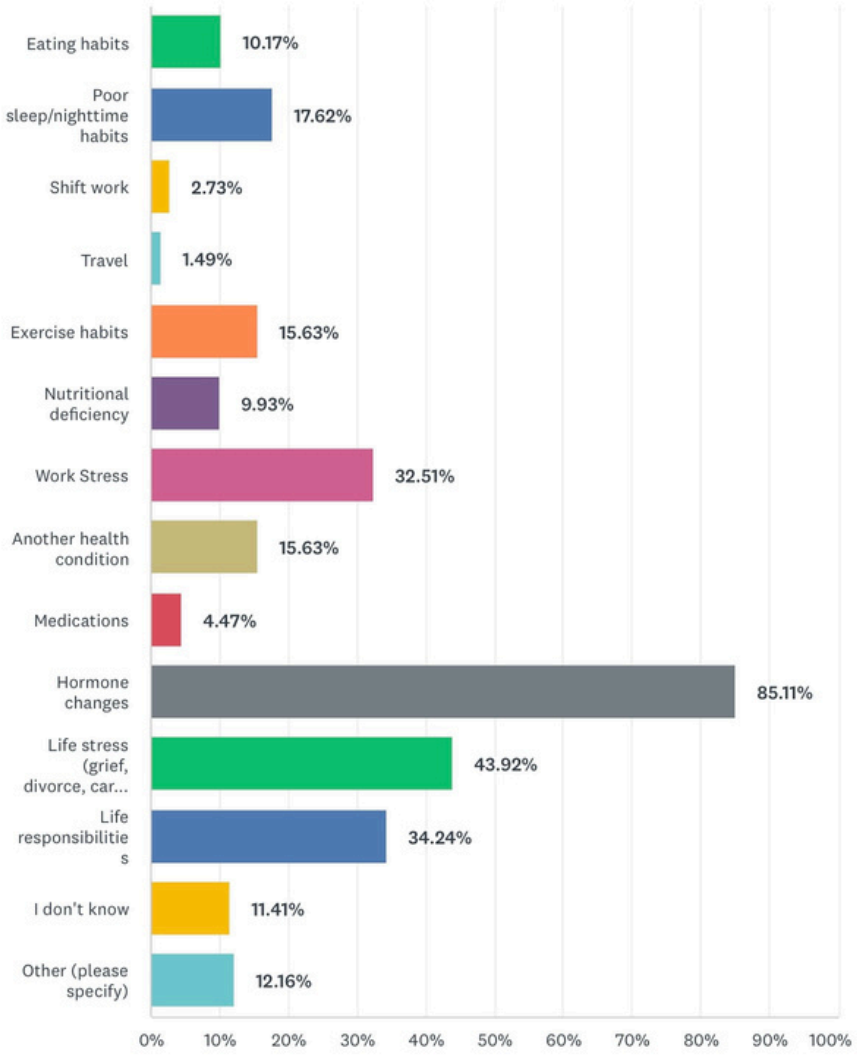
ANSWER CHOICES		RESPONSES	
Doctor/Naturopathic Doctor/Nurse Practitioner		71.96%	290
Pharmacist		4.71%	19
Registered Dietitian		2.48%	10
Sleep expert/clinic		12.16%	49
No one		22.83%	92
Other (please specify)	Responses	11.91%	48
Total Respondents: 403			

Q5

Customize Save as

What do you think could be the underlying cause(s) of your insomnia?

Answered: 403 Skipped: 1

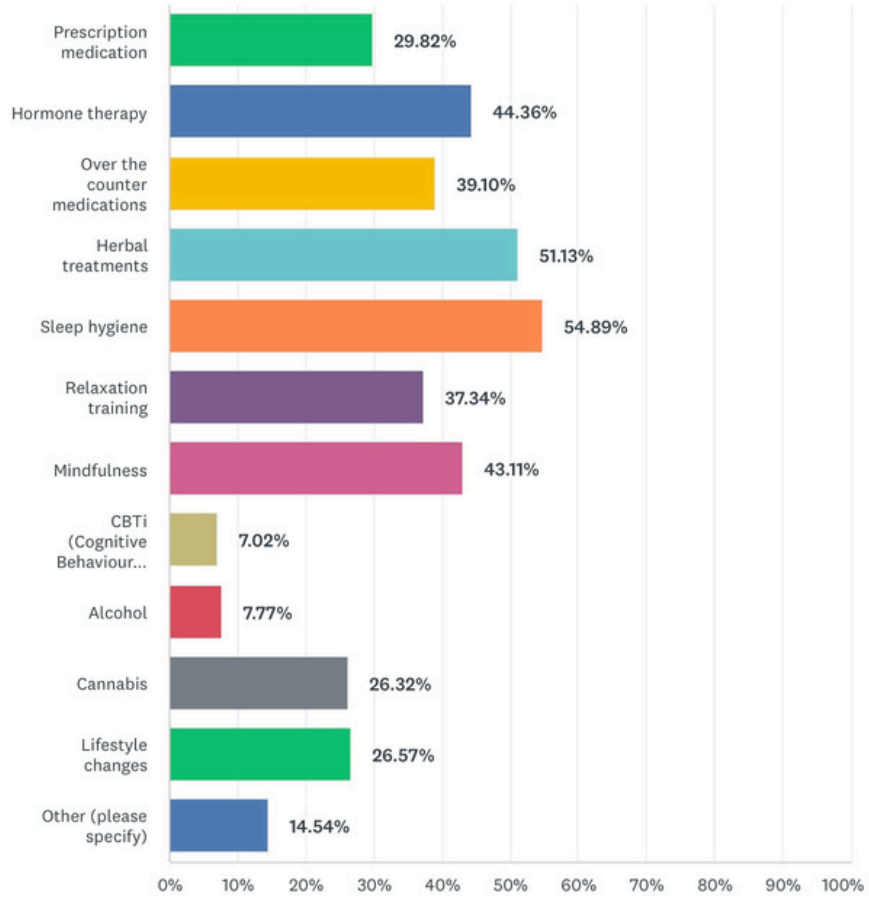


Q6

Customize Save as

What have you tried to improve your sleep and insomnia?

Answered: 399 Skipped: 5

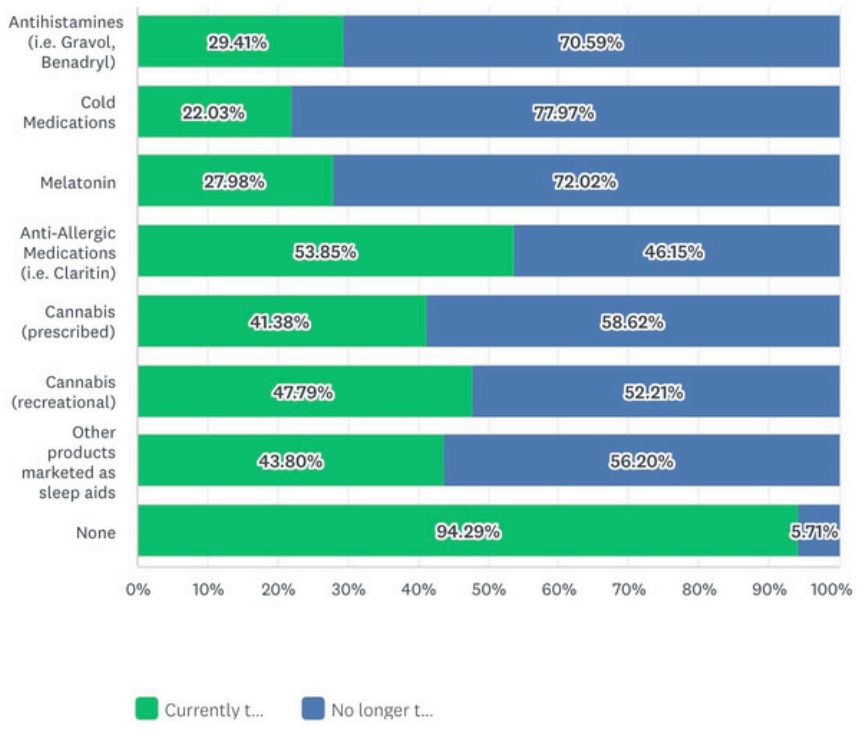


Q7

Customize Save as

Which over-the-counter sleep solutions have you tried?

Answered: 394 Skipped: 10



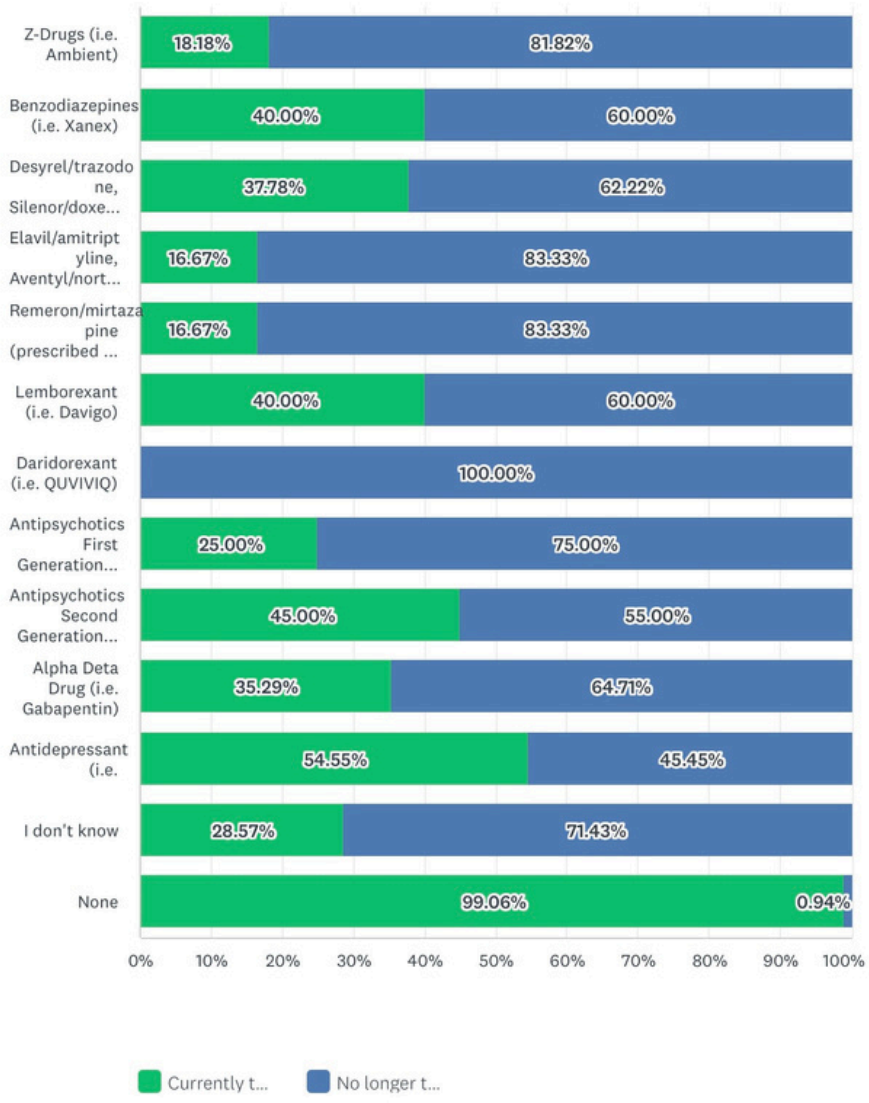
	CURRENTLY TAKING	NO LONGER TAKING	TOTAL
Antihistamines (i.e. Gravol, Benadryl)	29.41% 30	70.59% 72	102
Cold Medications	22.03% 13	77.97% 46	59
Melatonin	27.98% 68	72.02% 175	243
Anti-Allergic Medications (i.e. Claritin)	53.85% 28	46.15% 24	52
Cannabis (prescribed)	41.38% 12	58.62% 17	29
Cannabis (recreational)	47.79% 54	52.21% 59	113
Other products marketed as sleep aids	43.80% 60	56.20% 77	137

Q8

Customize Save as

Which prescription sleep medications have you tried?

Answered: 375 Skipped: 29

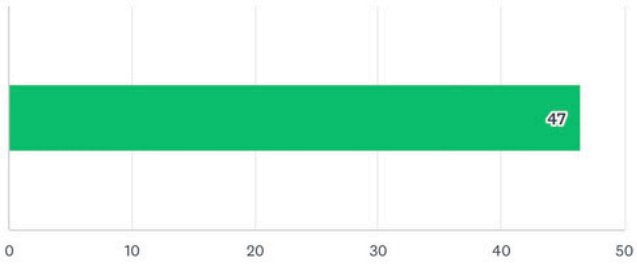


Q9

Customize Save as

How satisfied are you with your current management of insomnia? (0 = not at all satisfied, 100 = very satisfied)

Answered: 398 Skipped: 6



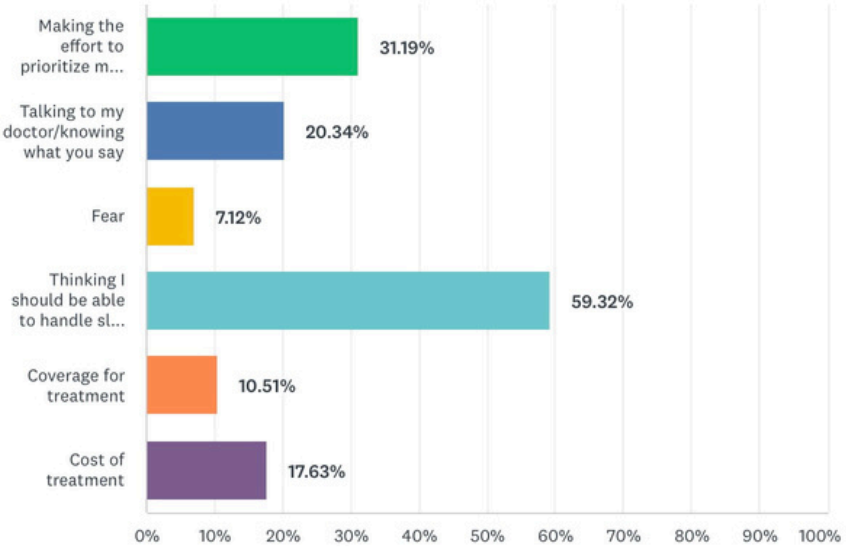
ANSWER CHOICES	AVERAGE NUMBER	TOTAL NUMBER	RESPONSES
Responses	47	18,511	398
Total Respondents: 398			

Q11

Customize Save as

What is the biggest challenge you have to achieving successful sleep?

Answered: 295 Skipped: 109



ANSWER CHOICES	RESPONSES	
Making the effort to prioritize my sleep	31.19%	92
Talking to my doctor/knowing what you say	20.34%	60
Fear	7.12%	21
Thinking I should be able to handle sleep on my own	59.32%	175
Coverage for treatment	10.51%	31
Cost of treatment	17.63%	52
Total Respondents: 295		

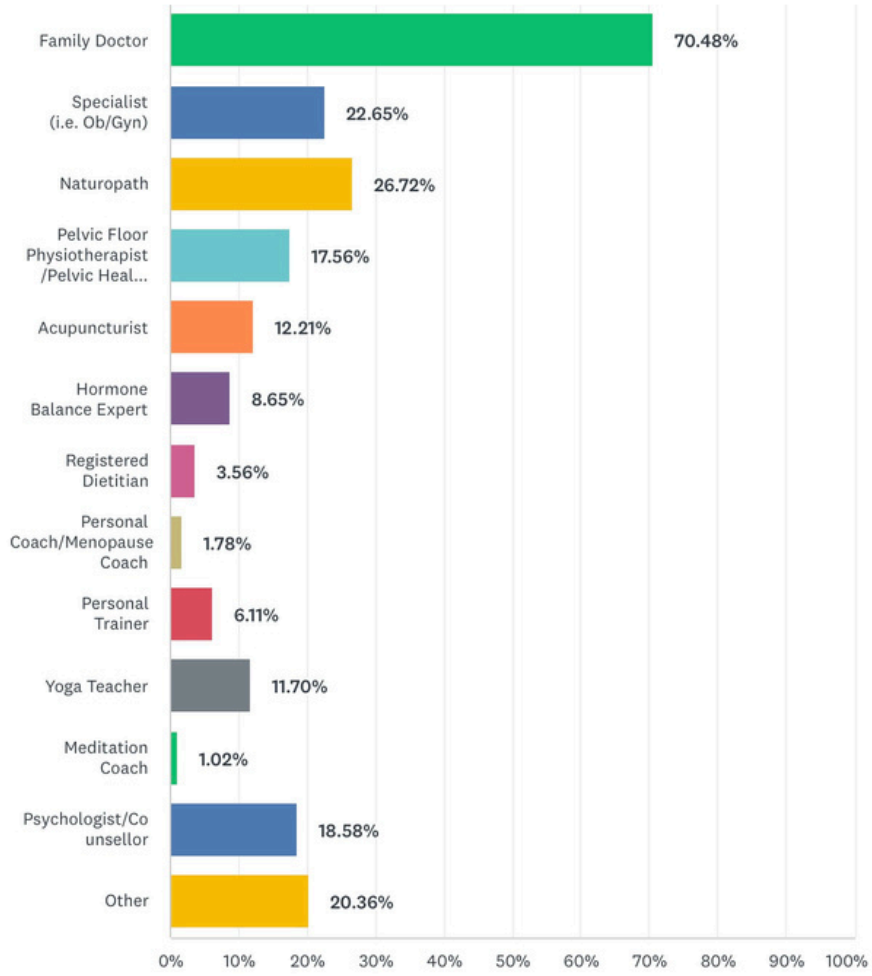
Comments (112)

Q19

Customize Save as

Who do you currently have on your midlife health team?

Answered: 393 Skipped: 11



Benefits coverage needs to better support people dealing with perimenopause & menopause.

I'm 13 years sober from alcohol and good sleep never really came back (at the time, they say it could take up to 2 years).

People my age need to be prompted to talk more about menopause and the challenges they experience. Too many suffer in silence.

It is difficult to find people in your area with the skills to build a good midlife health team and uncertain to what practitioners you need to support your needs.

I want people to understand the relationship between peri/post menopause and sleep apnea (not obstructive), as a contributor to sleep dysfunction, it's not just insomnia. And how it relates to low or sluggish thyroid

Very difficult to get information I'm comfortable with from my male family Dr. Always feel like I'm being told "it's nothing to worry about"

I desperately want to be able to sleep for more than 5 hours a night. It's been very frustrating that I've had to jump through all these hoops (ruling out sleep apnea, etc) and still she won't prescribe any type of sleep aid. Hoping the estrogen works. I did sleep last night...but sometimes I get the occasional good rest after many nights of only 5 hours.

Poor sleep makes everything else so much harder

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0862-000
Generic Drug Name (Brand Name): Daridorexant
Indication: Management of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.
Name of Clinician Group: Single Individual
Author of Submission: Alan Bell MD

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

I am an individual Ontario clinician with over 40 years of clinical experience in family medicine

2. Information Gathering

Please describe how you gathered the information included in the submission.

I am providing personal practice experience

3. Current Treatments and Treatment Goals

Please describe the current treatment paradigm for the disease.

Patients with long standing, nightly insomnia are very common, in fact seen almost every day in clinical family practice. Treatment goals are to improve sleep onset, sleep continuity, sleep duration ultimately to improve daytime functionality, alertness, mood and quality of life.

Current indicated treatment options include:

1. Cognitive behavioral therapy
2. Dual Orexin Receptor Antagonists (DORA) Includes daridorexant, drug currently under consideration
3. GABAergic sedatives (so call Z drugs)
4. Benzodiazepines
5. Doxepin
6. Non indicated drugs that are commonly used include
    a. Trazadone and other antidepressant and antiseizure medication
    b. First generation Antihistamines

c. Melatonin

d. SSRI/SNRI

e. Cannabis

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.

No medications in Canada are indicated for relief of chronic insomnia, the commonest clinical condition. CBTi is helpful, but not widely available or affordable to patients. Online apps and websites providing therapy are often to technical for many patients particularly the elderly (the commonest age group with chronic insomnia).

Available indicated drugs, particularly the benzodiazepines and GABAergic sedatives are only indicated for very short-term use. For example, the Zopiclone product monograph warning below renders these medications completely inappropriate for patients with chronic insomnia.

Treatment with IMOVANE should usually not exceed 7-10 consecutive days. Use for more than 2-3 consecutive weeks requires complete re-evaluation of the patient. Prescriptions for IMOVANE should be written for short-term use (7-10 days) and it should not be prescribed in quantities exceeding a 1-month supply.

These product warnings are completely appropriate, yet despite them, these drugs are very commonly prescribed by clinicians for long term use. This inappropriate prescribing results in tolerance, dose escalation and dependence.

Other indicated and non-indicated drugs listed above are limited by poor efficacy, next day sedation, intolerable side effects, dependence and limited on no clinical data supporting their use.

5. Place in Therapy

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

Daridorexant and other members of the DORA class specifically target chronic insomnia, and do not have a limitation of duration of use, do not induce tolerance or addiction and have demonstrated a superior side effect profile compared the other options. This includes less daytime sedation and better functioning.

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?

Patients with chronic insomnia need this medication. Treatment naïve patients will see the greatest efficacy and overall immediate and long-term benefit. Patients already on GABAergic will also benefit from this medication to assist them to taper and discontinue.

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?

Patient reported outcomes are what is used clinically. Specifically, sleep satisfaction, duration of sleep latency, frequency of wake after sleep onset, next day symptoms such as somnolence, mood, functionality are also critical outcome measures.

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

Unlike the GABAergic drugs no specific dependance or rebound issues need to be addressed. Patients can simply discontinue and revert to pre-treatment state.

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]?

This is an out patient drug to manage a chronic illness easily addressed by primary care clinicians.

6. Additional Information

The availability of DORA medication is a huge advance in the management of chronic insomnia. The inappropriate use of GABAergic drugs can be addressed by this class. Removing a financial barrier to patients is important to accomplish this.

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.

   No

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 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: Alan Bell
Position: Family Physician
Date: Nov 21, 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
Idorsia	x			
Eisai		x		
Add or remove rows as required				

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

CADTH

CADTH Reimbursement Review

Clinician Input

CADTH Project Number: **SR0862-000**
Generic Drug Name (Brand Name): daridorexant
Indication: Chronic Insomnia
Name of Clinician Group: ALEXANDER MELINYSHYN MEDICINE PROFESSIONAL CORPORATION
Author of Submission: Alexander Melinyshyn, MD, FRCPC

1. About Your Clinician Group

My name is Alexander Melinyshyn. I am a Royal College certified Neurologist (FRCPC), having completed my residency at the University of Western Ontario in 2018 with additional fellowship training in Headache Medicine (University of Calgary, 2019). I sit on the board of the Canadian Headache Society and the Scientific Committee of Migraine Canada. I operate a busy neurology practice with a particular emphasis on headache and chronic pain. I have extensive experience in the management of patients with complex and refractory headache disorders and often screen for and help manage sleep disorders as part of holistic care for my patients. I am already using the DORAs (dual orexin receptor antagonists) in my patient population with comorbid insomnia to great effect.

2. Information Gathering

The following input / recommendations are a combination of my personal clinical opinions based on my experience with treating patients and managing chronic neurologic conditions, supplemented by research articles (review articles, clinical trial data) from my personal review of the treatment described.

3. Current Treatments and Treatment Goals

In Canada, the landscape of sleep aid medications is complex, with a variety of options available (benzodiazepines, z-drugs, melatonin, H1-antagonists, antidepressants, and anticonvulsants) but few that are publicly covered under provincial healthcare plans. Despite their effectiveness in promoting sleep, there are no prescription sleep aids currently covered by public insurance plans in Canada for the treatment of chronic insomnia specifically, leaving patients to pay out of pocket for these medications unless they are part of a broader treatment for other conditions. As a result, many Canadians face financial barriers to accessing effective, ongoing treatment for chronic insomnia.

In order for a sleep medicine to be considered effective, it must improve the overall quality of sleep (common metrics include Sleep Latency (SL), Wake after sleep onset (WASO), Total sleep time (TST) and Sleep efficiency (SE)) but also result in improvements in patients' daytime function and their perception of fatigue or sleepiness (see s.5.3 for more details on clinical scales). Ideally, it would not cause a hangover effect or "grogginess" the following morning. The traditional sleep agents employed do not meet all of these ideals, or have potentially serious adverse outcomes with prolonged use (see below).

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.

While some of the agents we currently use for insomnia (medicines as above, CBT, sleep hygiene) work well for some, they do not work for every patient. Clinically, it is clear that there is a portion of the population experiencing chronic insomnia that requires other pharmacologic tools to optimize their well-being. Current sleeping pills, such as benzodiazepines and non-benzodiazepine hypnotics (e.g., zolpidem), are typically recommended for short-term use due to concerns about dependence, tolerance, and potential side effects. These medications can effectively induce sleep in the short run but are not considered safe for long-term use because the body may develop a tolerance, requiring higher doses to achieve the same effect. Current approaches do not modify the disease and in fact facilitate worsening of insomnia ("rebound insomnia") when discontinued abruptly, often requiring a protracted, gradual taper when patients wish to discontinue these medicines. Prolonged use is associated with an increased risk of cognitive impairment, falls, and other adverse health outcomes, especially in older adults. As a result, physicians generally reserve them for temporary sleep issues, such as those associated with acute stress or jet lag.

5. Place in Therapy

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

In contrast to the agents discussed above, newer sleep aids known as Dual Orexin Receptor Antagonists (DORAs such as daridorexant and lemborexant) are a promising class of medications designed to regulate sleep more naturally by targeting the orexin system which plays a key role in wakefulness. Unlike traditional sleeping pills, DORAs work by blocking orexin receptors, helping to promote sleep without significantly affecting other body systems. This mechanism reduces the risk of dependence and tolerance, making DORAs more suitable for long-term use. Clinical studies have shown that they can be safely used over extended periods without the same risks of cognitive decline or addiction, offering a potential solution for individuals with chronic insomnia who need ongoing treatment[1,2]. The DORAs as a class could reasonably be expected to cause a shift in the current treatment paradigm given these advantages.

While sometimes these drugs may be used concurrently with traditional sleep aids during a period of gradual cross-titration to prevent withdrawal / rebound insomnia, in general it is thought these would serve as effective single agent sleep aids for most individuals using them. Ideally, this class of medications would be considered first-line given its demonstrated efficacy, low side effect profile, and low risk for addiction and abuse. Given these significant advantages, I do not think it would be reasonable to require trials of traditional agents first – after all, you wouldn't make someone experiencing syphilis try topical mercury before advancing to the effective penicillin!

Helping with the underlying mechanism of insomnia: There is some limited evidence that the DORAs may help to modulate sleep architecture and continuity in ways that extend beyond traditional sleep agents. For example, suvorexant and lemborexant have been shown to increase total sleep time (TST), as well as the time spent *in all sleep stages*, in patients with insomnia[3,4]. Daridorexant, the most recent DORA available for patients with insomnia, was shown to improve sleep onset, sleep maintenance, subjective TST, and daytime functioning in two pivotal 3-month clinical studies[5]. Furthermore, additional studies found that daridorexant reduced both the number and duration of long awakenings across the entire 8-hour night[6]. The increase in sleep duration did not alter the proportion of time spent in NREM and REM sleep stages compared to placebo[5].

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?

Patients who are best suited for treatment with daridorexant generally include those who meet certain clinical criteria:

1. Adults with Primary Insomnia

Daridorexant is primarily approved for the treatment of primary insomnia, defined as chronic difficulty falling asleep or staying asleep without a clear underlying medical or psychiatric cause. It is most appropriate for patients who have trouble with sleep onset or sleep maintenance and do not have conditions like obstructive sleep apnea, significant depression, or anxiety disorders that could require

a different treatment approach. Typically, these symptoms persist for at least 3 months, despite trying behavioral approaches like sleep hygiene improvements.

2. Patients Who Have Not Responded Well to Non-Pharmacologic Treatments

Daridorexant may be considered for patients who have not achieved adequate symptom relief from behavioral therapies such as Cognitive Behavioral Therapy for Insomnia (CBT-I) or sleep hygiene interventions.

3. Patients at Risk for Dependence or Abuse

Since daridorexant does not have the same abuse potential as benzodiazepines or non-benzodiazepine hypnotics (e.g., zolpidem), it is considered a safer option for those at higher risk of substance use disorders or those who have struggled with medication dependence in the past. (Contrast with drugs like benzodiazepines or Z-drugs (e.g., zolpidem)).

4. Patients with Comorbid Sleep Disorders

Daridorexant has been shown to be effective for primary insomnia, but may also be helpful in patients with comorbid conditions that contribute to insomnia (e.g., depression or anxiety) when used as part of a broader treatment plan (e.g. employing SSRI/SNRIs).

5. Older Adults

Older adults (aged 65 and above) often experience sleep disturbances and may be more susceptible to side effects from other sedative-hypnotic medications. Daridorexant's relatively low incidence of next-day sedation and cognitive impairment may make it a better option for this population.

Key Contraindications and Caution for Daridorexant Treatment:

While daridorexant is generally well-tolerated, there are certain patients who may not be ideal candidates:

Severe Hepatic Impairment: Daridorexant should be avoided in patients with severe liver disease, as the drug is metabolized by the liver.

Hypersensitivity or Allergic Reaction: If a patient has shown a history of allergic reactions to daridorexant or any of its components, it should be avoided.

Concurrent Use with Certain Medications: Caution should be exercised when using daridorexant with other medications that affect the cytochrome P450 system (e.g., strong CYP3A4 inhibitors), as these could affect daridorexant's metabolism.

Pregnancy and Breastfeeding: It is not recommended during pregnancy or breastfeeding due to limited safety data.

***

Primary insomnia is a highly prevalent but underdiagnosed and undertreated condition with important ramifications for individual quality of life, work performance, and economic impacts. A Gallup poll (Gallup Organization for the National Sleep Foundation) suggested that only about 30% of patients experiencing insomnia mention it to their physicians, and only 6% of patients with insomnia seek treatment for it[7].

Patients may identify themselves when presenting to a health care provider, but given the low rates of spontaneous self-report, it is important for primary care providers and specialists to periodically screen for sleep disorders given their significant impact on quality of life and other disease states. This can be achieved by screening questionnaires at routine visits (see specific scales below). Polysomnography can be helpful as an adjunct in equivocal cases of insomnia or to clarify th presence of comorbid / confounding conditions, however it should not be required as a prerequisite for coverage, as the diagnosis of insomnia is mainly a clinical one.

It is not currently possible to identify those patients who are most likely to exhibit a response to treatment prior to actually trialling it based on our current modes of assessment.

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?

In order for a sleep medicine to be considered effective, it must improve the overall quality of sleep (common metrics used in clinical trials include Sleep Latency (SL), Wake after sleep onset (WASO), Total sleep time (TST) and Sleep efficiency (SE)) but also result in improvements in patients' daytime function and their perception of fatigue or sleepiness. Ideally, it would not cause a hangover effect or "grogginess" the following morning. The traditional sleep agents employed do not meet all of these ideals, or have potentially serious adverse outcomes with prolonged use (see below).

In a clinical practice, because of the high prevalence of insomnia and limited resources, it is not feasible to repeat frequent polysomnograms for patients undergoing treatment; the commonly employed scales sed to assess insomnia and progress in treatment include[8]:

1. Insomnia Severity Index (ISI)

- Purpose: To assess the severity of insomnia symptoms, including sleep onset, maintenance, early morning awakenings, and daytime impairment.
- Structure: 7 questions assessing the frequency and severity of insomnia.
- Scoring: Scores range from 0 to 28. Higher scores indicate more severe insomnia.

2. Pittsburgh Sleep Quality Index (PSQI)

- Purpose: To assess the overall quality of sleep over the past month, including sleep duration, disturbances, and daytime dysfunction.
- Structure: 19 questions covering sleep habits, sleep quality, sleep disturbances, and daytime sleepiness.
- Scoring: Total score ranges from 0 to 21. A score above 5 suggests poor sleep quality, which could indicate insomnia.

3. Epworth Sleepiness Scale (ESS)

- Purpose: To measure daytime sleepiness, which may be a consequence of insomnia or other sleep disorders.
- Structure: 8 questions assessing the likelihood of dozing off in different situations.
- Scoring: Scores range from 0 to 24. A higher score indicates more daytime sleepiness.

These scales are typically reassessed at 4-6 week intervals in the beginning of the treatment period, but once patients are stable, they can be reassessed every 6 months at the treating provider's discretion. The scales listed here are widely used because they are simple, effective, and help clinicians evaluate both the severity and consequences of insomnia. However, each of these has specific limitations and some explore items beyond the scope of what is commonly considered insomnia.

These scales generally align with endpoints assessed in clinical trials, especially the polysomnogram parameters previously mentioned. In particular, daridorexant made use of a scale called IDSIQ: the Insomnia Daytime Symptoms and Impacts Questionnaire developed by Hudgens and colleagues[9]. Studies closely following US Food and Drug Administration Guidance for Industry on patient-reported outcome measures, support use of the IDSIQ as a ft-for-purpose measure for deriving valid and reliable endpoints in insomnia clinical research trials and real-world studies. While this remains to be validated in a routine clinical setting, this scale improves on existing approaches to capture both nighttime and daytime impacts of insomnia and could easily be employed in primary care.

4. IDSIQ: the Insomnia Daytime Symptoms and Impacts Questionnaire

The IDSIQ typically includes items related to:

- Severity of insomnia (e.g., difficulty falling asleep, waking up too early, etc.).
- Daytime sleepiness or fatigue.
- Functional impact (e.g., work performance, social functioning).

Lower scores indicate better sleep and less impairment. Higher scores reflect more severe insomnia and greater daytime dysfunction. Total Score Interpretation:

- 0-10: Minimal to no insomnia or mild impact on daily life.
- 11-20: Mild to moderate insomnia with some daytime consequences (e.g., occasional fatigue or functional impairment).
- 21-30: Moderate to severe insomnia, with significant impact on daily functioning, including daytime sleepiness, fatigue, and cognitive difficulties.
- 31 and above: Severe insomnia with marked functional impairment.

For tools like the ISI or IDSIQ, clinically meaningful improvement generally refers to a score change that reflects a noticeable, beneficial difference in the patient's symptoms, specifically with regard to sleep quality, daytime sleepiness, and overall quality of life. While the specific criteria for a clinically meaningful change on the IDSIQ may vary depending on the study or context, it is generally accepted that a 10–20% improvement in score represents a clinically significant change. This is similar to other clinical measures where a 5-point or 20% reduction in total score would suggest that the intervention is having a meaningful impact.

.

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

Effectiveness: f the medication is no longer helping a patient to achieve better sleep, this may be a reason to discontinue it.

Adverse Effects: daytime drowsiness, dizziness, headache, or mood changes, it may be worth considering stopping the medication.

Interaction with Other Medications (P450-CYP3A4)

Change in Sleep Status: if the patient's insomnia has changed or improved (e.g., treatment for another condition), a patient may no longer need the medication.

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]?

Given that 20% of Canadian adults experience insomnia symptoms and 10-13 % meet the criteria for an insomnia disorder,[10,11] daridorexant prescription should not be limited to prescription by specialists alone given the prevalence of this issue and issues with specialist access nationwide. Patients may present to a wide array of providers with complaint of insomnia, it would be reasonable to provide prescription for this medication across settings inclusive of community clinics, hospital inpatient and outpatient settings, and specialty clinics like sleep medicine, psychiatry, neurology and internal medicine of all varieties.

Good sleep is crucial to total body health and overall quality of life. As a neurologist and chronic pain specialist, I see the ways in which disordered sleep intersects with a wide variety of conditions: headache, epilepsy, mood disorders, movement disorders, dementias and disorders of cognition… the list goes on. There are very few conditions that are not exacerbated by chronic insomnia, making clear the reason we spend a third of our lives asleep. In many instances, chronic insomnia may be holding patients back from recovering from their chief complaint. Take for example individuals with chronic migraine headache, who often experience increased headache frequency and severity due to poor sleep. Sleep deprivation can trigger or amplify headache attacks, leading to

a vicious cycle. In people with epilepsy, insufficient or fragmented sleep can lower the seizure threshold, resulting in more frequent and severe seizures. Similarly, mood disorders like depression and anxiety are closely linked with insomnia, as poor sleep can worsen symptoms such as irritability, cognitive impairment, and emotional dysregulation. The relationship between sleep disturbances and mood disorders is bidirectional, with each condition aggravating the other. Chronic insomnia not only contributes to the persistence of these comorbid conditions but also creates a complex cycle that is difficult to break without addressing both the sleep disturbance and the underlying conditions simultaneously.

Having access to new, safe, and effective sleep medications like DORAs is integral to providing holistic care for Canadians, as these treatments can help manage chronic insomnia, ultimately enhancing overall health and quality of life. I hope that your review will conclude in favour of coverage for this medication.

6. Additional Information

REFERENCES:

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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.

   No. I prepared this report independently.

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. I prepared this report independently.

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: Alexander Melinyshyn, MD, FRCPC (Neurol.)
Position: Clinic Director, Clinical Researcher
Date: 2024-12-18

☒ **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**
Idorsia	X			

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

I participated in an advisory board meeting in my capacity as a neurologist for specialty perspective on the mechanisms of this medication and how it might interplay with other neurologic conditions.

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0862-000
Generic Drug Name (Brand Name): Daridorexant (QUVIVIQ)
Indication: Insomnia
Name of Clinician Group: Canadian Consortium of Sleep and Sleep interested Physicians (CCSSP)
Author of Submission: Dr. Atul Khullar
Reviewers: Dr. Charles Samuels, Dr. Jennifer Swainson, Dr. Robert Cohen, Dr. Pratap Chokka, Dr. Marla Shapiro, Dr. Carmen Young, Dr. Lemore Alima, Dr. Omar Din, Dr. Ruth Baruch, Dr. Diane McIntosh, Dr. Manisha Witmans, Dr. Payman Hajiazim

1. About Your Clinician Group

This clinician group is comprised of a network of senior clinicians from British Columbia, Alberta and Ontario who have a very strong interest in the treatment of sleep disorders. The group includes nationally and internationally known specialist and family physician experts in sleep disorders, insomnia, menopause, mood, anxiety and attention deficit hyperactivity disorder (ADHD). All are extremely active in continuing medical education to public and professional audiences worldwide.

There are over 300 years of multi-disciplinary clinical experience among these clinicians that spans not only sleep medicine and insomnia, but general practice, psychology, and psychiatry. All have significant experience with the evolution, strengths, and weaknesses of treatments in insomnia disorder with and without multiple comorbidities, as well as a keen awareness of the longstanding gaps in treatment options for our patients.

Clinicians in the group also represent a wide variety of treatment settings, including hospital, community, and private outpatient settings. Most have academic appointments or university affiliations, and many are heavily involved in national and international research, clinical trials, as well as guideline development in insomnia and many of its major comorbid disorders.

2. Information Gathering

The information gathered for this submission was compiled from:

1. Significant group clinical experience with daridorexant in more than 2000 patients combined since its Health Canada indication and availability in the fall of 2023.
2. A review of the pertinent research data on insomnia disorder, current treatments and daridorexant.

Please note that there are three separate document files with this submission:

1. **This clinician input template**
2. **References**
3. **Financial disclosures**

3. Current Treatments

Insomnia disorder has been shown to be an independent clinical entity with clear diagnostic criteria. (1) It has a significant prevalence in Canada (over 13%) that is linked to medical and psychiatric illness as well as significant morbidity and health system costs. Over two thirds of patients are seen to have a chronic long term course. (2-4) Recent data put the estimated cost to the province of Quebec from insomnia alone at $6.6 billion yearly, mostly due to absenteeism, presenteeism and disability. (4) Insomnia disorder also has a bidirectional relationship with multiple common comorbid medical and psychiatric comorbidities such as cardiovascular disease, obesity, diabetes, major depressive disorder (MDD) and chronic pain (5) and the treatment of insomnia has been shown to improve these comorbid conditions. (6,7)

The first line therapy for insomnia disorder is cognitive behavior therapy (CBT-I), a short-term, sleep-focused, non-drug treatment. This includes sleep hygiene education, cognitive therapy, relaxation therapy, stimulus control and sleep restriction. (8,9) However, in the Canadian context, delivering this treatment is severely limited by lack of publicly funded access and training, as well as the limited number of adequately trained health-care providers competent to deliver treatment. Although it is quite efficacious with few adverse effects, and great leaps have been made to deliver this service through telemedicine strategies and digital therapeutics, many patients cannot or choose not to do CBT-I as it takes significant effort and motivation. Similar to lifestyle changes such as diet and exercise for weight management, patient adherence to CBT-I is limited. Up to 30% of patients also drop out of CBT-I therapy before finishing (10) and 30-35% of patients do not respond even after a full course of CBT-I treatment. (9,11) There may also be specific subtypes of insomnia that pharmacotherapy is be better suited for. (12, 13)

Hence, pharmacotherapy is a pillar of treatment and is the current practical standard of care for the management of insomnia disorder in Canada. Unfortunately, outside of the lemborexant, (currently non publicly reimbursed) this consists of a small range of drugs with safety warnings, limited evidence for efficacy, or agents that are used off label and have significant side effect burden such as weight gain. This leads to the inconsistent treatment of insomnia disorder. Accessibility to safer well tolerated pharmacotherapeutic agents with good evidence in the treatment paradigm for insomnia disorder are urgently needed.

Traditionally, the classes of drugs indicated by Health Canada for insomnia pharmacotherapy have included the benzodiazepines and the benzodiazepine receptor agonists (BzRA) zopiclone, zolpidem and eszopiclone, which have a similar but more specific mechanism of action. Although there are subtle differences between BzRA in their subunit binding patterns, all the above drugs work as sleep promoters through Gamma aminobutyric acid (GABA-A) receptor agonism.

Though effective, there are significant challenges to treatment of insomnia disorder with the benzodiazepines and to a lesser degree the BzRA. They can confer a significant risk of adverse effects, such as delirium, falls, motor vehicle accidents, respiratory depression, cognitive impairment, memory issues as well as abuse, dependence, tolerance, and withdrawal symptoms with long-term use, particularly in the elderly or medically ill. (14, 15) Insomnia disorder is also mostly a long-term chronic illness (16), yet treatment guidelines and large groups such Choosing Wisely and deprescribing.org recommend against the use of these drugs in the long term. (8, 17-19). These recommendations for short term use of indicated insomnia medications, leaves clinicians in a quandary for long term treatment options in chronic insomnia.

And though the evidence does not completely support this, Health Canada monographs and regulatory colleges in many provinces have also put punitive dispensing restrictions and excess monitoring on the benzodiazepines and BzRA, (20-25) making clinicians even more hesitant to treat insomnia disorder with them. Despite a different mechanism, better safety profile and promising data, another indicated option (low dose doxepin) has not been proven

to be widely successful in its clinical use and only has an indication for sleep maintenance. (26) It is also not publicly reimbursed in Canada.

More recently, two other agents that work very differently have been indicated for insomnia treatment. They assist sleep by blocking the novel wake promoting neurotransmitter orexin and have excellent long-term safety and efficacy data, with very few of the major issues that plague many of current indicated treatments. These dual orexin receptor antagonists (DORA) include the drug currently under review, daridorexant, and lemborexant, which is not publicly reimbursed.

Because of the above limitations and lack of reimbursement, unfortunately numerous drugs without Health Canada approval or good evidence are routinely used in the treatment of insomnia. By necessity, they often become a first line treatment for many Canadian clinicians. Commonly used ones that have mixed recommendations include the hormone melatonin and the sedating antidepressant trazodone. (27, 28)

Many other off label agents are also utilized, and these include sedating antidepressants (mirtazapine, amitriptyline), other members of the benzodiazepine class (lorazepam, clonazepam), alpha-2 delta ligand anticonvulsants (gabapentin and pregabalin) and the mostly inappropriate usage of low dose atypical antipsychotics (quetiapine, olanzapine, risperidone). **Though guidelines indicate that these can be useful in insomnia disorder cases with significant comorbid illness or certain subpopulations, (27) evidence is scant, many have side effects such as significant weight gain, and these are not usually recommended treatments.** (8,17,18, 29)

Patients often resort to self-medication of their insomnia disorder with poorly regulated over the counter (OTC) preparations containing doxylamine, dimenhydrinate and diphenhydramine (3) These can also lead to tolerance, dependence, falls and other deleterious cognitive side effects, especially in the elderly. (30-32) Surveys also indicate a high use of patient self-medication using substances such as alcohol and cannabis for insomnia. (33) Outside of very rare usage of cannabis for sleep difficulties associated with significant comorbidities, (34) the use of cannabis for insomnia disorder can be a dangerous practice, yet it is common and heavily promoted by the legalized retail and medical cannabis industry. **All the above factors lead to a confusing landscape and at times mistreatment for many Canadian patients suffering from insomnia disorder.**

The underlying disease mechanisms of insomnia disorder are still being investigated and are complex and multifactorial. No pharmacological treatment appears to modify the disease mechanisms, and all medication treatment at this point should be considered symptomatic. However, early prompt treatment may reduce further chronicity and disability of insomnia disorder. (27) CBT-I directly targets the perpetuating factors contributing to the chronicity of the disorder and may thus be considered to partially modify the underlying mechanisms. (35) Other off label treatments may facilitate a reduction and improve insomnia symptoms by treating the underlying comorbidity and CBT-I has been shown to do this as well. (7, 36)

4. Treatment Goals

Current treatment guidelines for insomnia disorder are centered around 2 primary goals. One is to improve sleep continuity [i.e., nocturnal symptoms such as improving sleep onset, sleep maintenance by reducing awakenings and increasing the total sleep time (TST)] and more importantly, to improve related daytime function [i.e. decreases in fatigue, impaired attention/concentration, disrupted mood, lack of motivation and improvement in social impairments. (17).

By definition, treatment of insomnia disorder would not provoke adverse effects such as next day cognitive impairment, unsteadiness or behavioral abnormality occurring during sleep. Simply improving nocturnal symptoms is not adequate if

not achieving an improvement overall daytime function. Normal sleep architecture should be preserved and restored as much as possible as well.

Insomnia is related to many adverse health consequences including depression, cardiovascular disease, hypertension, obesity, and neurodegenerative disease. (37-39) Optimal management of insomnia should also have a significant positive impact on burden on these diseases, overall occupational function, and health related quality of life.

5. Treatment Gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Insomnia is a multifactorial complex disease, and it is well known that not all patients respond to all treatments. Unfortunately given the currently indicated treatments, it has long been a “one size fits all” approach for the Canadian clinician which has not previously considered the variety of insomnia symptom types, mechanisms, and associated comorbidities.

As mentioned previously, CBT-I is an excellent first line treatment, but is often not accessible or acceptable to the patient and has a limited response rate even when used optimally. Hence pharmacotherapy is a critical clinical intervention -- either in tandem, after, or instead of this first line treatment. Many of the currently approved medications have potential side effects that limit their use in several populations. Long term efficacy is often undocumented and only 4 agents, daridorexant, lemborexant, eszopiclone and zolpidem have data of 6 months or more. (40-44) None of these are publicly reimbursed in Canada.

Even when used properly as per the current evidence, current treatments such as benzodiazepines and to some extent the BzRA, commonly show a significant lack of response, tachyphylaxis and tolerance in clinical practice. Outside of the small group of Canadians that have access to the non-publicly reimbursed lemborexant, clinicians have not had a consistently safe and evidence based treatment for chronic insomnia. **As result, an unfortunate common practice includes prescribing scheduled drugs at doses and durations that guidelines and monographs do not support. Alternately, off label agents with potentially burdensome side effects are used, or insomnia disorder is trivialized and not treated appropriately.**

Given this and the wide use of OTC products and substances by patients for sleep, it is quite clear outcomes are not being met in insomnia disorder. Treatments with better evidence on key outcomes with improved tolerability and safety are critical. Compliance with medication is typically not an issue, however both psychological and physical dependency with certain agents can be problematic.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

As noted above, could be argued that most patients with chronic insomnia disorder have an unmet need. Insomnia disorder is very common and presents frequently to the primary care physician. Almost one-third of visits to a family practice network were related to a sleep complaint and 11% met the criteria for insomnia disorder, (45) which is remarkably consistent with the Canadian population prevalence data of 30-35% for a sleep complaint and more than 13% for the disorder. (3) Equitable access to another accessible, tolerable, and efficacious approved treatment such as daridorexant is absolutely necessary to give further options for the Canadian clinician to address this common and disabling complaint, especially in chronic insomnia.

Particular groups of patients with a greater unmet need would include.

a. **Groups at greater risk and prevalence of insomnia disorder.** This includes women, shift workers, individuals with chronic pain, and patients with comorbid medical and psychiatric disorders such as depression, anxiety, ADHD and bipolar disorder. (46-48). Patients with mental health comorbidities have also been seen to improve significantly with daridorexant in a recent open trial (49) and this dovetails with our clinical experience.

b. **The elderly and hospitalized patients.** Older patients have a high rates of insomnia disorder that can lead to many deleterious outcomes such as falls, cognitive decline and dementia (50, 51). Only doxepin, lemborexant and daridorexant have shown safety and efficacy for insomnia disorder in this group. (52-55) There has been no indication of fall risk with daridorexant and the DORA class, a problem with older sleep agents. (56) Eszopiclone, a newer BzRA has some degree of efficacy and safety in the elderly, (57) but belongs to a class of medications that has proven troublesome in the past. There is also some thought that the mechanism of the DORA such as daridorexant would lead to more favourable response in the elderly as the insomnia disorder in this group may be more related to orexin dysfunction. (58) We have seen this in our clinical experiences as well.

   Yet again, none of these agents are on public formulary in any Canadian province, which leads to suboptimal prescribing choices for insomnia disorder in the elderly. This is especially pertinent in hospital settings where many patients are given off label and potentially dangerous agents for their insomnia. More equitable access to daridorexant and other medications with safety and efficacy data in the elderly is critical for Canadian clinicians working with patients in acute and long-term care facilities.

c. **Patients with substance abuse, especially to alcohol or opiates:** There are strong bidirectional relationships between substance abuse and insomnia (59) and sleep disturbances are a strong risk factor for relapse in substance use disorders. (60) Yet these patients have even more limited options as the benzodiazepines and BzRA drugs to a lesser degree can promote dependence and are usually not recommended for these groups of patients. Daridorexant has not been classified as a controlled substance by Health Canada and there is no evidence of potential or actual substance abuse issues with this drug, (61) hence it and the DORA have become natural options for these patients in our clinical practices

d. **Patients on regularly prescribed opiate medications:** The benzodiazepines (and BzRA drugs to a lesser degree) lead to potential increased risk for potentially lethal respiratory depression, mortality and severe respiratory events when used in conjunction with opiates. (62) Although there is no data yet in conjunction with opiates, daridorexant does not appear to have any impact on respiratory depression (63-65) and appears to have limited adverse effects at supratherapeutic doses consistent with potential overdose. (66) Daridorexant is often used clinically by this group as an option for treating insomnia in these patients.

e. **Patients with chronic insomnia disorder requiring long term pharmacotherapy:** As noted above, only four agents; daridorexant, lemborexant, zolpidem have controlled trial data of greater than 6 months. (40-43). In particular, daridorexant has long term controlled double blind clinical trial data up to 12 months, which includes data to support improved next day function and quality of life. (43) Unfortunately, none of these agents are publicly reimbursed, creating a disconnect between the evidence and accessibility for treatment of chronic insomnia disorder.

f. **Patients under 18:** There are no indicated treatments for insomnia disorder in this group

g. **Patients with comorbid insomnia and sleep apnea** – Though the data does not always support this, especially for the BzRA drugs (67, 68) Health Canada monographs indicate that both BzRA and benzodiazepines are

relatively contraindicated in this group (20-23), limiting treatment options. The comorbidity of sleep apnea and insomnia (COMISA) is common and is likely a significant more indolent phenotype of the disease demonstrating higher rates of morbidity as well as risks of comorbid disorders such as depression and cardiovascular disease. (69-71) Although CBT-I is the first line treatment and has shown efficacy in this group, (72) clinically daridorexant has become a natural choice if pharmacotherapeutic treatment for COMISA is required because of the data showing no worsening of sleep apnea or other breathing disorders. (63-65)

6. Place in Therapy

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

As noted above, daridorexant is a DORA (Dual Orexin Receptor Antagonist) which is a unique, novel, and more specific mechanism of action. It is part of a new evolving paradigm of medications with high pharmacological specificity to offer improved safety, efficacy, and more targeted symptom outcomes in insomnia disorder.

This competitive and transient dual orexin receptor antagonism targets a completely different cerebral network in comparison to almost all other medications used both on and off label for insomnia. It directly and specifically targets the mechanism of high wakefulness and hyperarousal during the night which may be more related to the underlying disease process of insomnia disorder. It does this in a precise fashion without almost any other effect on other neurotransmitter areas. (73) This is in direct contrast to most other indicated agents that promote inhibitory neurotransmitters and/or crudely and non-specifically suppress indirect arousal mechanisms. It also appears to increase total sleep time in a more natural fashion by increasing all the stages of sleep equally. (74, 75) as well as not create balance and cognitive problems when waking up from sleep. (76)

Daridorexant is clearly a first line therapy for all patients with chronic insomnia disorder that are offered pharmacotherapy. It has clinical trial data in comorbid and elderly populations demonstrating excellent short- and long-term efficacy/tolerability, a favorable side effect profile, (43, 55, 77, 78) no apparent tolerance, withdrawal, or dependence, (60) and limited overall next day effects, even on driving. (79). Daridorexant is recommended by Italian and European Insomnia treatment guidelines (80, 81) and has gained an favorable recommendation from the treatment of long term insomnia from the prestigious United Kingdom's National Institute of Clinical excellence (NICE) (82). Meaningful changes in objective measures of quality of life and total sleep time have also been seen with daridorexant (83, 84).

Daridorexant also demonstrates limited drug interactions and no change in dosing or adverse events is suggested in wide age and weight groups. (85, 86) Even though the FDA classified it as a schedule IV drug, there is no compelling evidence of abuse potential in theory (61), seen in clinical trials or in a number of years of use in the United States, Europe or Canada. Health Canada has not classified it as a controlled substance.

A clearly favorable benefit risk ratio has been seen for daridorexant (87, 88). A recent comprehensive meta-analysis evaluating all insomnia treatments indicated that daridorexant had one of the highest probabilities of being the best treatment for objective sleep outcomes. (89)

Our clinical experience has also matched the above trial data and our group strongly views daridorexant as a first line agent for chronic insomnia disorder pharmacotherapy for all Canadian clinicians.

Although the unique mechanism of daridorexant would complement other insomnia pharmacotherapy, combination pharmacotherapy for insomnia disorder would be off label and saved for more resistant patients or those with multiple

comorbidities. In these scenarios using combination therapy, our group has found that though both agents are used, lower doses of other medications with a higher side effect burden may be used, thereby lowering the overall risk.

Pharmacotherapy can also often complement CBT-I and may facilitate earlier insomnia remission (90, 91). Given the unique mechanism of action and the lack of tolerance, rebound, and withdrawal with daridorexant, extrapolation from other studies would the support concomitant use of daridorexant and CBT-I. We have also commonly seen that the unique mechanism of daridorexant complements other pharmacological treatments for common comorbid conditions such as depression and bipolar disorder, as it does not interfere with the mechanism of action of drugs used to treat those disorders and does not increase side effects.

The availability and usage of the daridorexant and the DORA class has already caused a shift towards better treatment of chronic insomnia disorder in the current treatment paradigm. We have seen hundreds of patients who have discontinued less proven or riskier medications, cannabis, OTC products or alcohol to help their symptoms. Daridorexant could be considered benzodiazepine and BzRa "sparing," as previously clinicians would have no choice but to use other medications long term in an off-label fashion to treat the patient, constantly having to weigh the risks of the agent versus treatment of the disorder.

Earlier, safer treatment of chronic insomnia disorder has been seen with the first line use of daridorexant, which may reduce chronicity and the aforementioned wide ranging health consequences of the disease. More equitable access for daridorexant would further this paradigm shift. This access would be sustainable to the Canadian health care system because the agent is priced very competitively in this country for a novel mechanistic agent, especially given the significant economic burden of insomnia. This group has had many patients who have had no qualms for paying out of pocket for daridorexant given the marked improvement in their functioning, cognition and limited next day side effects.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

Patients should always be offered or trialed on some form of CBT-I, or at the very least stimulus control and sleep restriction as a first line treatment, as this is an efficacious non-drug long term intervention with very few adverse effects. After this, given that major comorbidities have been assessed and treated, daridorexant would be a first choice pharmacotherapeutic treatment for all chronic insomnia patients given the data on efficacy, tolerability, safety and potential unique mechanism of action that may be disease modifying.

Lemborexant, the other indicated DORA in Canada, lemborexant has many similar features to daridorexant and could also be considered a first line treatment, However, daridorexant appears to carry fewer side effects (88) and both DORA work differently on the orexin receptors. (85) **We have clearly seen that both DORA medications need to be tried for a particular patient and response to one does not predict response to the other.** Accessibility to both agents is necessary for effective clinical treatment of chronic insomnia disorder.

Other BzRA, especially eszopiclone, which has a wide variety of efficacy and safety data in multiple populations superior to the other non DORA insomnia medications (92, 93) could be considered for short term/acute insomnia or second line treatment for chronic insomnia. Doxepin could be considered, especially in the elderly if sleep maintenance is an issue. (53) Trazodone and melatonin have some guideline support and could be considered. (27, 28) Other off label treatments could still be considered if there is a major comorbid condition to be treated (27), failure of the above treatments, or if financial access to newer agents is an issue. Though other medications may be used, there are not that supplant daridorexant and the DORA class as a first line treatment for chronic insomnia.

6.3. How would this drug affect the sequencing of therapies for the target condition?

As mentioned above, daridorexant and the DORA class has allowed us to use treatments such as benzodiazepines, BzRa and off label treatments such as trazodone and mirtazapine later in therapy. The safety and tolerability profile of daridorexant and the DORA class clearly differs from those of more traditional sleep-promoting drugs. (94)

If daridorexant and the DORA class fail, the risk benefit ratio of other agents is more defensible for patients and clinicians. Other drugs could be used as a subsequent second or third line of therapy if the patient is stable on that treatment and has been offered CBT-I initially or concomitantly. Off label combination use of daridorexant and other agents for sleep has proven to be useful clinically.

6.4. Which patients would be best suited for treatment with the drug under review?

Data formally identifying of subgroups that will preferably respond to daridorexant is still unclear. As this drug acts in a mechanism to "turn off the wake signal", (95) clinically it is hypothesized that it may work well for patients suffering states of hyperarousal, such as those with chronic pain, mood disorders, anxiety disorders, or trauma related conditions.

Many of the other groups that would be clinically well suited to daridorexant have a great unmet need for treatments and have been outlined above in question 5.2. To reiterate this would include:

a. **Patients who don't respond, or are unable or unwilling to do CBT-I.** – As noted above, this is a high percentage.

b. **The elderly** – As mentioned in question 5.2, given the unsuitability of many other agents because of further cognitive impairment and fall risk. This has matched our clinical experience.

c. **Patients with comorbid neurodegenerative diseases** – Orexin system dysfunction appears to be related to both Alzheimer's disease and frontal temporal dementia. (96, 97) Though this is a complex dynamic process that has yet to be fully clarified, it appears that DORA may help chronic insomnia disorder in these patients. (98)

d. **Individuals with comorbid substance abuse issues** – There is emerging evidence linking orexin dysfunction with the biology of addiction (99, 100) and we have seen clinically that daridorexant uniquely helps many patients with chronic insomnia disorder and comorbid substance use disorders that would have been excluded from clinical trial data sets.

e. **Hospitalized or other patients at risk of falls** – Recent data indicate very low rates of postural stability change in next day and middle of the of the night dosing with daridorexant. (76) with no signal for falls. (56). This is a direct contrast to almost any on and off label psychotropic medication used for sleep. (101) Increasing sleep time overall may also mitigate the fall risk seen with decreased sleep. (102)

f. **Patients with untreated or potential obstructive sleep apnea (OSA) or chronic obstructive pulmonary disorder (COPD)** – Data supports use of daridorexant in patients with OSA or COPD without worsening those conditions (63-65).

g. **Individuals who are on opiate painkillers** – Daridorexant does not worsen airway dynamics, so may also be clinically suited to patients on opiate painkillers as noted in question 5.2.

h. **Patients who have evidence of complex sleep related behaviours –** Over 3% of patients on the BzRA zopiclone and zolpidem (103) demonstrate complex sleep related behaviors, and it is also outlined as a class effect warning in the monograph for the BzRA drugs. (20-23) Although vivid dreaming and nightmares have occasionally been reported with daridorexant, the agent has not shown any evidence of producing complex sleep related behaviours in the clinical trial data or in the clinical experience of this group.

i. **Patients who wish to receive assistance in z-drug/benzodiazepine/sedative deprescribing due to emerging deleterious effects or lowering the potential risk of them.** – A small clinical trial and our experience have noted that a significant number of patients can switch to daridorexant quite easily, (104) though cross titration is typically necessary.

Actual disease characteristics that would indicate suitability for daridorexant treatment would includ chronicity of disease given it is one of only three indicated sleep agents that has efficacy data for up to 12 months (40-43). Given the reduction of hyperarousal by daridorexant, we have also found clinically that patients that have disorders of the arousal system (such as insomnia disorder comorbid with anxiety depression, bipolar disorders, ADHD, post-traumatic stress disorder (PTSD), and chronic pain syndromes appear to respond better.

6.5. How would patients best suited for treatment with the drug under review be identified?

The diagnosis of insomnia disorder is made with history taking, clinical examination and judgment. Although there are clear criteria, insomnia disorder is also a longitudinal illness often accompanied by many comorbid, sleep, medical and/or psychiatric disorders. (29, 105, 106) **The insomnia complaint can be a risk factor, separate disorder or symptom of its major comorbidities as almost ¾ of patients have at least one major comorbidity. Regardless, the insomnia needs to be treated and often requires separate treatment even when there is a comorbidity** (1, 45) Patient reporting of subjective symptoms can be prone to selection and/or recall bias, hindering the diagnosis. Depending on training and experience there can be much variability in expert opinion on the interpretation of the contribution of insomnia disorder in a particular patient's overall case. Subsequent over or under attribution to comorbid conditions often occurs.

There are no laboratory tests to diagnose insomnia disorder, however validated diagnostic tools have been developed such as the Insomnia Severity Index to assist diagnosis and treatment monitoring (107, 108). There are also other scales to establish the likelihood of other sleep disorders that include the STOPBANG and Berlin questionnaire (sleep apnea), IRLS (restless legs syndrome) and the MEQ (circadian rhythm disorders). (109) Common comorbidities such as depression, anxiety, bipolar disorder, and ADHD need to be screened for as well and tools such as the PHQ-9, (depression) GAD-7, (anxiety), MDQ (bipolar disorder) and the ASRS (ADHD) can be used. (109) However, these are all subjective scales that lack specificity to create a diagnosis and there is variability in usage and comorbidity screening. This does not preclude the treatment of insomnia, especially with CBT-I, but not assessing comorbidities can potentially greatly reduce the effectiveness of all treatments. Simple monitoring with sleep diaries and movement-based technologies is also popular clinically.

Often a polysomnogram or sleep study (PSG) is used to rule out other sleep disorders but is not recommended routinely for insomnia workup (106). Full PSG testing is superior in this facet, but not widely accessible in many parts of the country without cost or significant wait times. Home PSG testing is notoriously inaccurate in the setting of insomnia disorder and the overutilization of this can interfere with an insomnia workup and incorrectly judge the contribution of a breathing related sleep disorder, jeopardizing the order in which the insomnia disorder is treated.

Insomnia disorder is not challenging to diagnose properly in clinical practice, but a major issue is the lack of understanding of how its many medical, sleep and mental health comorbidities interact to ensure proper treatment. System issues in diagnostic and treatment difficulties are related to a lack of primary care training, full PSG and insomnia specialist support in parts of Canada. **Provinces outside of Ontario often only have one or two centers that treat insomnia patients, and the treatment of chronic insomnia needs to be made easier for primary care prescribers. Better reimbursement of safe and effective treatments for chronic insomnia is one way to help reach that goal.**

It is unclear if there is an insomnia prodrome, but early and prompt intervention with CBT-I or short-term medications in the acute phase intuitively can lessen disability in the future. (110)

6.6. Which patients would be least suitable for treatment with the drug under review?

Least suitable patients would include those who have not responded to multiple attempts with other agents (daridorexant may be tried, but expectations would be guarded) and who have not had formal behavioral sleep medicine interventions. Other less suitable patents would include those with a high degree of untreated comorbidity, pediatric patients as there are no data, or patients with narcolepsy type illnesses that already lack orexin would not be suitable.

There is also no data for daridorexant in the transient insomnia patient that requires as needed sleep medication, and the mechanism of action would likely be more suited to a chronic insomnia that requires regular pharmacotherapy. Nonetheless, many of this group have found clinical success in off label as needed use, especially in shift workers.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

This sort of response specificity has remained elusive in insomnia disorder, although further work with more specific agents such as daridorexant as well as insomnia phenotypes may eventually change this. Since daridorexant transiently inhibits the wake and arousal system, intuitively, patients who have this disruption may respond better. As previously noted, clinically this group has seen better responses in many areas where arousal is disrupted such as patients with insomnia and MDD, anxiety, ADHD, PTSD, and fibromyalgia. The elderly may also have a type of insomnia that responds to the orexin blocking mechanism of action (58). The group has also seen that those without long term benzodiazepine or BzRA use may do somewhat better, indicating again the potential suitability of daridorexant as a first line therapy.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Outcomes used in clinical trials include objective measures of sleep on the PSG such as LPS, TST, wake after sleep onset (WASO) as well as similar variables calculated by subjective patient sleep diary measures. TST is thought to be most correlated to self-report next day function. (111)

The Insomnia Severity Index (ISI) is the most frequently used patient reported outcome to document treatment response and remission from insomnia in clinical trials. This scale correlates well with outcomes used in clinical practice which would be self-reported improvement in insomnia symptoms, sleep quality, nighttime wakening, amount of sleep, next day fatigue, and ultimately, daytime functioning and quality of life. (108)

6.9. What would be considered a clinically meaningful response to treatment?

There has been a lack of standardization of clinically meaningful outcome measures in insomnia clinical trials (112), and there may be a mismatch between subjective and objective definitions of response and remission. (113) However, when using the ISI, which is a 7-item patient-report scale with a maximum score of 28, a cutoff score above 8 or 10 have been used to indicate clinically significant insomnia disturbance, and a score of below 8 is used to indicate the absence of insomnia. A score greater than 14 suggests moderate to severe insomnia (109, 110). In clinical trials of both CBT-I and pharmacologic agents, a change in the total ISI score of 7 or greater indicates a clinically meaningful improvement of insomnia symptom severity, whereas a change in the absolute value of the ISI score to below 8 points indicates a remission from insomnia. (108)

Although there can be great variability, commonly used definitions of objective response are the LPS or WASO values of below 30 min, sleep efficiency over 80% as well as an increase of TST over 30 minutes. Daridorexant at 50 mg is equivalent or above clinically significant effect sizes for these subjective and objective variables compared to other indicated pharmacotherapeutic agents for sleep (83, 89, 114)

In support of assessing clinically meaningful outcomes, a new validated daytime functioning scale has been developed for insomnia. The **Insomnia Daytime Symptoms and Impacts Questionnaire (I**DSIQ) assesses daytime symptoms and impacts that have been reported as more clinically meaningful for patients than traditional measures such as hours of sleep. (115, 116). Daridorexant clearly showed improvements in all domains of this patient centered functional outcome in short- and long-term clinical trials (43, 77, 81, 84).

The magnitude of response to treatment can vary greatly by physician in insomnia disorder. Factors include recognition of insomnia disorder as a separate dimension that requires treatment, training in treatment modalities for insomnia, the ability to assess, screen and get major comorbidities treated, adherence to guideline-based therapy, therapeutic rapport with patient, as well as the availability of full PSG and CBT-I resources.

6.10. How often should treatment response be assessed?

This depends on the severity. When treatment is initiated, response should be assessed every 2-4 weeks to monitor response, especially if concomitant CBT-I is being pursued or there are significant changes to pharmacotherapy. If a patient remains stable, review every 3-6 months would be warranted. (27) Because daridorexant is not associated with tolerance, long term side effects or tachyphylaxis, assessment of treatment response in chronic insomnia is less frequent than when other agents such as benzodiazepines or BzRa drugs are used due to side effects and evolving risks. (14) We have found using daridorexant and DORA drugs reduces service utilization in our practices.

6.11. What factors should be considered when deciding to discontinue treatment?

Factors to be considered include both level and stability of response and the key outcome how the sleep leads to improved next day function. Lack of response in this area would lead to discontinuing treatment. Conversely, a very positive response may also lead to consideration of discontinuing treatment if concomitant CBT-I has been used or if the response is longstanding and stable. Daridorexant has no evidence of physical withdrawal and can be stopped quickly making it much easier to discontinue treatment compared to the benzodiazepines and to a lesser extent BzRA. Stopping these drugs quickly can lead to numerous deleterious psychological effects and even seizures. (14) Other factors that lead to discontinuing daridorexant are uncommon adverse events such as excessive next day fatigue, disturbing dreams and rarely sleep paralysis.

6.12. What settings are appropriate for treatment with the drug under review?

This is an oral tablet that does not need supervision. It can be taken in all settings (hospital inpatient/outpatient, community settings or at home by the patient)

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

No, as noted above, insomnia and chronic insomnia are an extremely common disorders, presenting in some fashion to most clinical specialties. Daridorexant is a safe, tolerable agent that can easily be used by any physician that needs to treat chronic insomnia with pharmacotherapy. Most commonly this would be the community prescribers, family physicians, psychiatrists, or sleep specialists, but could include prescribers in a variety of other specialties including such as pain medicine, women's health, or obesity medicine. Given its favourable efficacy and safety in the elderly, geriatric physicians, hospitalists and internal medicine specialists may initiate treatment as well. No special monitoring is required for the prescription and long term use of this medication.

7. Additional Information

Daridorexant is a very safe, effective, and tolerable first line agent suitable for a wide age range of people who suffer from chronic insomnia, which is a serious and common condition that can lead to significant morbidity, mortality and health system costs if not adequately treated. **This group strongly believes that the data for daridorexant accurately reflect our clinical experience, and it has become a much needed and valuable 1st line pharmacotherapy for chronic insomnia disorder in a wide variety of settings. It is easy to prescribe and is competitively priced for a novel mechanistic agent with excellent efficacy, safety and functional outcome data.**

Daridorexant has been found to be very helpful alone or in combination to treat those with chronic insomnia associated with medical and psychiatric comorbidities. Numerous patients often will report "the most natural sleep I have had," "felt the most rested I have ever felt," and "finally I have gotten the sleep I have been wanting for so long." Significant improvements in function and return to work from disability has been observed. Clinicians themselves suffering with insomnia have reported similar benefits from taking daridorexant.

More equitable access to this agent will allow better and earlier treatment of insomnia disorder. This will reduce the current byzantine pantheon of off label medication, self-treatment with OTC products and use of recreational substances for insomnia disorder that has far more deleterious effects on the patient and the health care system.

8. 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.

No.

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.**

See attached disclosures

DECLARATION FOR CLINICIAN

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.**

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Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range (for previous 48 months)**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
NONE	☐	☐	☐	☐

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Abbvie	☐	☒	☐	☐
Boehringer	☒	☐	☐	☐
Eisai	☒	☐	☐	☐
Idorsia	☐	☒	☐	☐
Ingelheim	☒	☐	☐	☐
Janssen-Ortho	☒	☐	☐	☐
Lundbeck	☒	☐	☐	☐
Otsuka	☐	☒	☐	☐
Sprout	☒	☐	☐	☐
Sunovion	☒	☐	☐	☐
Takeda	☒	☐	☐	☐

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Eisai	☐	☒	☐	☐
Lundbeck	☐	☒	☐	☐
Otsuka	☐	☒	☐	☐

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Eisai	☐	☐	☒	☐
Idorsia	☐	☐	☒	☐

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NONE	☐	☐	☐	☐

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Eisai	☒	☐	☐	☐
Novartis	☒	☐	☐	☐
Paladin	☒	☐	☐	☐
Sunovion	☒	☐	☐	☐

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Bausch Health	☐	☐	☒	☐
Canopy Health	☐	☒	☐	☐
Eisai	☐	☐	☒	☐
Elvium	☐	☐	☒	☐
Idorsia	☐	☐	☒	☐
Jazz Pharma	☐	☒	☐	☐
Lundbeck	☐	☐	☒	☐
Otsuka	☐	☐	☒	☐
Paladin Pharma	☐	☒	☐	☐
Takeda	☐	☒	☐	☐

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Janssen-Ortho	☒	☐	☐	☐
Lundbeck	☒	☐	☐	☐
Otsuka	☒	☐	☐	☐

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Eisai	☒	☐	☐	☐
Idorsia	☒	☐	☐	☐

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Eisai	☒	☐	☐	☐
Idorsia	☒	☐	☐	☐

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Bausch	☐	☒	☐	☐
Eisai	☐	☐	☒	☐
Idorsia	☐	☐	☒	☐
Lundbeck	☐	☐	☒	☐
Otsuka	☐	☐	☒	☐

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Novartis	☒	☐	☐	☐
Vivos	☒	☐	☐	☐

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NONE	☐	☐	☐	☐

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CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: <SR0862-000>
Generic Drug Name (Brand Name): <Daridorexant or Quviviq>
Indication: <Insomnia>
Name of Clinician Group: <Family Physician Airways Group of Canada>
Author of Submission: <Alan Kaplan>

1. About Your Clinician Group

Family Physician Airways Group of Canada (www.fpagc.com)

<Enter Response Here>

2. Information Gathering

Experience with the medication and revie of literature

<Enter Response Here>

3. Current Treatments and Treatment Goals

Chronic insomnia, be it a primary disorder in itself or secondary to other medical condition, is common and causes great patient distress and even disability. The current insomnia treatment paradigm includes non-pharamacologic therapies such as sleep hygiene and CBTi (cognitive behavioral therapy for insomnia) which is rarely actually available in Canada.

As far as pharmacologic therapies

No drug class other than DORA (direct orexin receptor antagonist) are indicated or reimbursed for chronic insomnia

DORAs have a unique mechanism and Daridorexant has an improved safety margin vs Lemborexant with regard to receptor binding and less incidence of sedation and nightmares.

Current pharmacological options are limited to short-term use in terms of safety and current Canadian drug indications

The risk-benefit ratio of currently available short term pharmacological options when used long-term in chronic insomnia clearly favor DORAs due to side effects of what is otherwise available including sedation, fall risk and cognitive worsening.

Another key factor is the safety margin for hypnotic therapies in those with Obstructive Sleep Apnea(OSA), particularly untreated. Current non-DORA treatments will worsen the OSA while studies have shown the safety in even the untreated OSA population with DORAs

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.

Please describe goals (needs) that are not being met by currently available treatments. Examples of unmet needs:

- Not all patients respond to available treatments
- Patients can become refractory to current treatment options such as benzodiazepines and Z drugs due to tolerance
- No other treatments are available to reverse the course of disease of chronic insomnia disorder
- No treatments are available to address the key outcome of next day functioning
- Treatments are needed that are better tolerated and safer than current treatments which do not have long term indications (Z drugs and benzos) or no sleep indication at all (trazadone, cannabis, gabapentin, quetiapine and others)
- Treatments are needed to improve complianee
- Formulations are needed to improve convenience

5. Place in Therapy

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

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Yes, it is a unique mechanism as a direct orexin receptor antagonist to reduce ‘wakefulness’ cf causing sedation.

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Yes to some degree in primary CID (chronic insomnia disorder), with the potential to assist in sleep and help in many comorbid conditions

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

First line for CID

Would the drug under review be reserved for patients who are intolerant to other treatments or in whom other treatments are contraindicated?

No, however it should replace many current inappropriately used therapies

Is the drug under review expected to cause a shift in the current treatment paradigm?

The shift is already happening, but many cannot pay for it due to coverage

Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with drug under review. Please provide a rationale for your perspective.

No, not if we are treating chronic insomnia disorder that has been properly assessed

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?

Which patients are most likely to respond to treatment with drug under review?

Chronic insomnia disorder, primary or secondary

Which patients are most in need of an intervention?

All who require pharmacotherapy

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

No

How would patients best suited for treatment with drug under review be identified (e.g., clinician examination/judgement, laboratory tests (specify), diagnostic tools (specify))

Historical illness, measurement tools include Insomnia Severity Index (ISI)

Are there any issues related to diagnosis?

Need to rule out medication causes, obstructive sleep apnea eet

Is a companion diagnostic test required?

no

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

No

Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review?

No current evidence to predict responders in CID.

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?

Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Yes, ISI

What would be considered a clinically meaningful response to treatment? Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Reduction in ISI, but most importantly improving next day function

Examples: improved survival; reduction in the frequency/severity of symptoms (provide specifics regarding changes in frequency, severity, etc.); attainment of major motor milestones; ability to perform activities of daily living; improvement of symptoms; and stabilization (no deterioration) of symptoms.

<Enter Response Here>

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

Due to tolerance to current treatments a cross titration of increasing the DORA and reducing the other medication will be needed.

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]?

Any and all, this does not need specialty care other than for sleep studies when deemed necessary by tools such as STOP-BANG and Epworth Scales

6. Additional Information

Is there any additional information you feel is pertinent to this review?

<Enter Response Here>

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.

   No

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 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.**

   Astra Zeneca, BI, Covis, Eisai, GSK, Idorsia, Merck Frosst, Moderna, NovoNordisk, Pfizer, Sanofi, Trudel, Valeo

Declaration for Clinician 1

Name: Alan Kaplan
Position: Chairperson, FPAGC
Date: Nov 20, 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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			

Other companies do not have sleep treatments				

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

Declaration for Clinician 2

Name: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
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 3

Name: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
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 4

Name: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
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 5

Name: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
Add company name				
Add company name				
Add or remove rows as required				

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

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0862-000
Generic Drug Name (Brand Name): Daridorexant (Quviviq)
Indication: Insomnia
Name of Clinician Group: Lakeridge Health Oshawa Hospital (Mental Health and Addictions)
Author of Submission: Marcel Wagner, Inpatient Mental Health Pharmacist

1. About Your Clinician Group

We are a community hospital network in the Durham region, Ontario Home - Lakeridge Health

2. Information Gathering

Daridorexant Canadian monograph - [Product Monograph Template - Standard]

Delphi consensus recommendations for the management of chronic insomnia in Canada - ScienceDirect

Sleepwell | It's no dream. Sleep well without sleeping pills.

Impairment Rating Scale

3. Current Treatments and Treatment Goals

Adult Insomnia

- A very debilitating and underdiagnosed condition complicated by other sleep impairments including RLS, RBD, OSA, etc
- CBT-I is first line, Dual Orexin Receptor antagonist (DORA) - Lemborexant and Daridorexant are the only approved chronic sleep medications to help give restorative sleep by reducing sleep fragmentation by shutting down the wakefulness Orexin system that is often active at night with insomnia with no tolerance or additive potential
- Mirtazapine, Trazodone, Melatonin, Diphenhydramine, Quetiapine, Z-drugs such as Zopiclone/Eszopiclone/Zolpidem and Benzodiazepines are often used to produce sedation to help with sleep. None are approved for chronic insomnia management, and most have either tolerance or substantial side effects. Mirtazapine (weight gain, RLS), Trazodone (priapism, not recommended by US/CAN Sleep societies), Melatonin (circadian rhythm, RBD management), Diphenhydramine (anticholinergic effects/sleep fragmentation). Doxepin (Silenor) low dose 3mg and 6mg are safer doses but may have limited efficacy
- DORAs help to get to the root cause of the physiologic aspects of insomnia. The Orexin system is implicated in worsening sleep. Daridorexant can reduce daytime sleepiness and may reduce cardiac and diabetes complications. Several mental health conditions may be better managed when sleep quality and quantity are improved
- Getting access to CBT-I can be difficult but should be utilized whenever possible. The benefits may take some time but should be pursued even if sleep medication is required. Daridorexant is both safe and effective with no tolerance or abuse potential. It is also safe in Obstructive Sleep Apnea (OSA)

- Good sleep is the cornerstone to both physical and mental wellbeing. Daridorexant and other DORAs continue to be studied but the potential for reducing delirium, accidents, substance use, cardiac and diabetic issues, depression, anxiety, bipolar disorder, psychosis relapses along with many other conditions requires everyone to protect sleep and do everything in their power to get good quality and quantity of sleep. Evidence of the importance of sleep is becoming more apparent as it continues to be studied.

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 of therapy and unmet needs

- Insomnia is not properly assessed or diagnosed regularly: consider offering patients to fill out the Insomnia Severity Index screener and for all health care practitioners to ask about sleep and daytime functioning
- Too much emphasis is made on specific conditions without taking into account sleep. Depression and anxiety often have an aspect of sleep impairment that should be treated independently of either condition. Pain perception can be improved or worsened by insomnia and mood therefore treating sleep can reduce perception of pain
- Sleep quality and quantity worsen as people age and can cause a lot of impairment
- We need to find treatments that are both effective and tolerable (DORAs have no tolerance, addiction potential and appear to be safe taken chronically
- The current digital age has increased screen time for those of all ages which can worsen sleep
- Daridorexant and other DORAs help both sleep onset and sleep maintenance. Fall risk appears to be reduced likely due to improved daytime functioning and sleep duration and quality (ie less fragmented sleep)

The current limitation to current therapies is tolerance and increase risk of abuse and withdrawal. Most therapies such as Z-drug and benzodiazepines can be used for short term use effectively, but patients tend to have a harder time stopping if continued more than 2 weeks. Many prescribers find it difficult to stop providing a prescription for short term insomnia treatment. Daridorexant and other DORAs can be effectively used long term along with CBT-I.

5. Place in Therapy

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

Daridorexant is a Dual Orexin Receptor antagonist just like Lemborexant which has been available in Canada since 2021. DORAs are a unique class of sleep medications that can be taken along with other types of medications.

This medication gets to the root of the problem of Insomnia by acting on the Orexin wakefulness system and blocking it during the night when it should not be active which will reduce fragmented sleep and improve the quality and quantity of sleep to improve both NREM and REM sleep with appropriate sleep cycles (ie epochs)

Daridorexant is considered a second line therapy behind first line CBT-I but because it is both safe and effective, it should be considered (along with Lemborexant) as the only chronic sleep medication to be used in conjunction with CBT-I whenever possible

Dual Orexin Receptor Antagonists such as Daridorexant and Lemborexasnt are causing a huge paradigm shift in sleep medicine. Previously, only CBT-I was recommended for chronic insomnia, but prescribers have been forced to used off label treatments that can be effective for a short time but often have long term negative risks. mysleepwell.ca comments about how sleep medications can cause detrimental problems long term but DORAs are quite different and should not be put in the same category as these other

sleep medications. All other sleep medications have minimal effectiveness and cause many side effects along with tolerance/withdrawal. DORAs such as Daridorexant and Lemborexant are starting to be used to help wean patients off longterm Z-drug and Benzodiazepine use as there are no tolerance or withdrawal effects with DORAs

CBT-I should be tried but after that Daridorexant or Lemborexant should be used due to their safety and tolerability profile while targeting the Orexin system.

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?

Patients with clinical insomnia and that have either failed or do not have access to CBT-I should be considered for this medication. Most patients respond well to DORAs (including Daridorexant). Obstructive Sleep Apnea patients with Insomnia are especially at an additional risk of health complications and this medication is compatible with CPAP.

Patients who are at risk of or have multiple medical, mental health and substance use issues may have the most benefit from this treatment.

Using the Insomnia Severity Index clinical screener along with a thorough clinical examination and sleep history will be helpful for diagnosis – ask patient about sleep habits (sleep latency and maintenance) and daytime drowsiness vs function

Insomnia is underdiagnosed and usually treated too late. CBT-I is not utilized enough and short term therapies are unfortunately used chronically along with off label treatments.

Most patients will respond to DORA therapy but will need to be given education that sedation is no longer the goal and improved daytime functioning needs to be a core goal

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?

Improving quality and quantity of sleep along with daytime functioning will be similar as seen in being tested in clinical trials

A clinically meaningful response to treatment is a more restorative and refreshing sleep which will help with overall quality of life and improvement of most medical, mental health and substance use disorder complication

An improvement in sleep may even help reduce the incidence of cognitive impairment over the lifespan. Studies continue to show the importance of sleep for all aspects of life

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

Daridorexant can be taken chronically by most individuals and is very safe and tolerable. Consider discontinuation if there is no longer a need for the medication (eg CBT-I alone is helpful).

5.5 What settings are appropriate for treatment with Daridorexant? Is a specialist required to diagnose, treat, and monitor patients who might receive Daridorexant?

Most community practitioners have the ability to diagnose adult insomnia. Refer to a sleep specialist or neurologist for more complex cases such as concurrent OSA, RLS, RBD. Geriatricians may find this medication very effective as it can reduce the risk of falls and be helpful in helping to wean off problematic medications that are on the Beers list.

6. Additional Information

DORAs are a very new and interesting way of treating insomnia. Daridorexant is a good sleep medication with maximum safety and minimum side effects.

7. Conflict of Interest Declarations

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

No, all answers are solely my own

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, I looked up all the information myself

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: Marcel Wagner
Position: Hospital Pharmacist
Date: 20-12-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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 Canada	X			
Takeda Canada	X			
Otsuka Lundbeck Canada	X			

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

Declaration for Clinician 2

Name: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
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 3

Name: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
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 4

Name: <Enter full name>
Position: <Enter currently held position>

Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
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 5

Name: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
Add company name				
Add company name				
Add or remove rows as required				

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

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0862-000
Generic Drug Name (Brand Name): Quviviq
Indication: <Enter Response here> Chronic Insomnia Disorder
Name of Clinician Group: MedSleep
Author of Submission: Joseph michaels

1. About Your Clinician Group

I am a sleep medicine physician. I work with MedSleep. A sleep medicine organization that treats the full spectrum of sleep disorders.

2. Information Gathering

Patient interactions
Manufacturer publications
Real world experience

3. Current Treatments and Treatment Goals

- Currently the only medications approved for Chronic Insomnia disorders are Benzodiazepines and Z-drugs
- Other non-indicated medications include selective antidepressants and over the counter medications
- None of the current medications that are used without the indications for insomnia and recommended by the American Academy of Sleep Medicine
- The current medications used target the GABA- pathway
- The treatment goals would be to decrease the symptoms of chronic insomnia disorder to less than 3 times /week and improve daytime functions, have the most accessibility and affordability and the least amount of side effects. They should be used safely especially in the elderly population.

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.

1- The current pharmacotherapeutic agents for treatment that are available for treatments are generally associated with dependance and risk of cognitive side effects. They are generally not safe in the elderly population. The non-pharmacological options such as CBT-I are not usually OHIP-funded and generally inaccessible

5. Place in Therapy

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

Quviviq would be a very safe alternative to many of the medications currently used. It specifically targets insomnia. It targets the Orexin pathway, which none of the current medications used do.

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?

Which patients are most likely to respond to treatment with drugs under review? Patients suffering with chronic insomnia disorder that are not responding to proper sleep hygiene. It will benefit many age groups due its prolific safety profile. This medication is not appropriate for intermittent or as needed use. It is best used for Chronic Insomnia disorder

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' self reported improvement in duration and quality of sleep, daytime functioning and ISI scale. It should be assessed in the beginning every 4 weeks, then every 3 months thereafter.

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

Patients' side effects such as daytime functioning, nightmares or sleep paralysis.

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]?

This is highly appropriate in the hospital setting, outpatient setting, nursing home, dementia facilities. A specialist should not be needed to diagnose and treat the condition.

6. Additional Information

I think it is really important to highlight the safety profile of this medication and the paucity of drug-drug interaction.

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. No

<Enter Response Here>

2. No

<Enter Response Here>

3. Idorsia

Declaration for Clinician 1

Name: Joseph Michaels, MD
Position: Medical director of the Niagara snoring and sleep center, Pediatric director in the Toronto sleep institute, pediatric director in Thornhill sleep institute.
Date: 17 Dec 24

X **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		Idorsia		
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: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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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
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 3

Name: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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
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 4

Name: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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

.

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 5

Name: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
Add company name				
Add company name				
Add or remove rows as required				

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

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: **SR0862-000**
Generic Drug Name (Brand Name): **daridorexant**
Indication: Chronic Insomnia Disorder
Name of Clinician Group: BC Psychiatrists with Expertise in Sleep Medicine
Author of Submission: Michael Butterfield MD, MSc, FRCPC (Psychiatry and Pain Medicine)

1. About Your Clinician Group

Our clinician group is a collaboration of psychiatrists that have a special interest or subspecialty training in sleep medicine.

2. Information Gathering

The information gathered in this submission includes data from daridorexant clinical trials and the review of studies on the incidence of insomnia disorders and the impact these disorders have on patient outcomes.

3. Current Treatments and Treatment Goals

In 2002, an estimated 3.3 million Canadians (13.4% of the household population aged 15 or older) had insomnia. A US study in 2012 that investigated the incidence of chronic insomnia found an incidence rate of 9.3%. General treatment measures for chronic insomnia include the treatment of comorbid medical and psychiatric conditions, modifying sleep-interfering medications and substances, and optimizing the sleep environment. Specific treatments for insomnia fall into two primary categories; non-pharmacological and pharmacological therapies. Non-pharmacological therapies, largely cognitive behavioral therapy for insomnia (CBT-I) is the gold standard treatment for this disorder. Medications for chronic insomnia disorder are considered mainly in patients who are unable to participate in CBT-I or who still have symptoms despite participation in such treatments. In terms of pharmacological treatment, there ate currently no medications that are approved in Canada for treatment of chronic insomnia. Currently, clinicians are forced to use medications that have been shown to have efficacy in the treatment of insomnia disorder, though most of the studies that show positive patient outcomes are short in duration (< 4 weeks). Currently, non-benzodiazepines (zopiclone, zolpidem), antidepressants (doxepin, trazodone, L-trytophan), benzodiazepines (temazepam), and over-the-counter supplements (melatonin, Valerian root) are recommended as first-line pharmacotherapy though the quality of evidence to support their use is low to moderate. . Other drugs, such as sedating antidepressants or anticonvulsant medications are recommended as second- or third-line agents, particularly when comorbidities (e.g. mood disorder or epilepsy) are present.

Current treatments to not modify the underlying disease mechanism but rather exert their effect by increasing inhibition in the central nervous system to decrease hyperarousal and induce sedation. These treatments have proven short-term efficacies; however, their long-term effectiveness diminishes soon after cessation of therapy. Benzodiazepines and other hypnotics are known to create physical dependence in patients undergoing long-term treatment, and termination of treatment can lead to withdrawal symptoms lasting for months. Conversely, daridorexant targets the underlying pathophysiology of insomnia by binding orexin receptors and inhibiting the action of the neuropeptide orexin, which is secreted primarily in the lateral hypothalamus and exhibits its effects by activating two G protein-coupled receptors, orexin receptors type one and type two. Orexin functions to promote daytime wakefulness and is largely inactive during sleep. Daridorexant helps patients get to sleep and stay asleep longer by competitively binding both orexin receptors, preventing the downstream effects of orexin. This medication has been shown to lead to positive changes in important clinical outcomes including decreased wake time after sleep onset, latency to persistent sleep, increased total

sleep time and decreased daytime sedation and improved daytime function. Furthermore, these medications have significantly less side effects compare to the current treatment options available to patients and do not have the risk of dependency that benzodiazepines and other sedating medications do.

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 are no currently Health Canada approved medications that are available to Canadians for treatment of chronic insomnia disorder other than daridorexant.
- Currently there are few pharmacological treatment options for insomnia for older adults (>65 yo) that do not have significant increased risk of cognitive impairment, sedation and increased falls risk.
- Patients can become dependant on or develop a sedative use disorder with the current guideline recommended medications for treatment of insomnia disorder.
- Patients become refractory to current treatment options
- Treatments are needed that are better tolerated
- Treatments are needed to improve compliance
- As noted above the current treatments for chronic insomnia have only been shown to be efficacious in trials lasting < 4 weeks. The current medications are known to create physical dependence in patients undergoing long-term treatment, and termination of treatment can lead to withdrawal symptoms lasting for months. Patients with any comorbidity that involves respiratory depression or are on other sedating medications for their comorbid illnesses, such as chronic pain, are unable to be treated with the current guideline recommended medications.

5. Place in Therapy

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

Daridorexant would be used as a first-line treatment for chronic insomnia disorder as it is one of only two medications on market in Canada that have that has shown to be effective for > 4 weeks in phase three clinical trials.

Daridorexant could be recommended for patients who are intolerant to other treatments or in whom other treatments are contraindicated though it would be ideal for this medication to be used as a first-line treatment over the current recommended medications due to the superior side effect profile and reduced risk of dependency.

Daridorexant is expected to cause a shift in the current treatment paradigm to use orexin modulating medications as first line treatments for chronic 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?

Patients that are most likely to respond to treatment with daridorexant are those with moderate to severe insomnia disorder without other comorbid sleep disorders, substance use disorders or severe psychiatric illnesses. Patients that are most in need of this treatment are those that meet the above criteria and not only are not suitable for CBT-I but also have comorbid medical illnesses or take medications that result in significant risk of harm if they only have access to the current sedative medications used for treatment if insomnia.

Chronic insomnia is a clinical diagnosis and to identify if a patient has this disorder physicians are recommended to:

- perform clinical assessment where they administer a sleep disorders questionnaire

- assess and optimize the management of any underlying medical, psychiatric or environmental cause that could be contributing to insomnia symptoms. This is a critical component of the assessment as not addressing this can lead to overdiagnoses of insomnia disorder.
- instruct the patient to complete a sleep diary
- Assess the severity of insomnia using validated scales such as the Insomnia Severity Index, Epworth Sleepiness Scale or STOPBANG

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 improvements in sleep variables seen with daridorexant in the pivotal phase 3 study of this medication include both a statistically significant reduction in sleep latency and an improvement in sleep maintenance. At month 3 in this study, daridorexant use resulted in a statistically significant increase in total sleep time of approximately 1 hour and a mean duration of 6.5 hours of sleep. These results are in line with treatment goals for the management of chronic insomnia in clinical practice and are considered clinically meaningful outcomes. Further, statistically significant improvements in mood, alertness and cognition domains were seen with the use of daridorexant.

The magnitude of these clinical effects would likely be able to be measured by specialists and general practitioners.

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

Factors that would be considered when deciding to discontinue treatment with daridorexant include:

- Lack of response to treatment (no clinically significant change in sleep latency, maintenance, or total sleep time)
- Lack of functional benefit despite sleep outcomes improved
- Development of intolerable or severe side effects (sleep paralysis, hallucinations, suicidal ideation, nasopharyngitis, headache or excessive daytime sleepiness)

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]?

Community settings, hospitals (inpatient and outpatient clinics), and specialty clinic

A specialist would not be required to diagnose, monitor and treat patients who receive this medication.

6. Additional Information

None.

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.

No.

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: Shaohua Lu MD FRCPC
Position: Clinical Associate Professor UBC
Date: 18/12/2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
Idorsia		X		
Eisai			X	

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

Declaration for Clinician 2

Name: Michael Butterfield MD FRCPC
Position: Clinical Assistant Professor, UBC
Date: 18/12/2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
AbbVie	X			
Novartis	X			

Teva	X			
Eisai	X			
Lilly	X			

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

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: **SR0862-000**
Generic Drug Name (Brand Name): Daridorexant
Indication: Insomnia
Name of Clinician Group: Mood Disorders Research and Treatment Service, Providence Care Hospital, Kingston, Ontario
Author of Submission: Dr. Ruzica Jokic

1. About Your Clinician Group

Mood Disorders Research and Treatment service is a subspecialized clinic for patients with treatment resistant mood disorder in adults. We deal with patients with multiple co-morbidities including sleep disorders. We have a population of over 800 active patients at any time point.

2. Information Gathering

Dr. Jokic has extensive experience in treatment and research of sleep disorders and have done multiple educational presentations in Insomnia, sleep disorders and their interface with mood and medical disorders. We have treated tens of thousands of patients with Chronic insomnia disorder (CID) as a primary focus of the patient presentation as well as a part of the presentation of depression or Bipolar disorder, for more then 20 years.

We became familiar with orexin antagonists over the last several years. Dr. Jokic has a specific interest in CID and worked closely with my colleagues to obtain knowledge in their mechanism of action, indications for use and safety profile, since these medications were approved in Canada. We obtained experience in clinical benefit sand side effect profile of daridorexant for the treatment of CID.

3. Current Treatments and Treatment Goals

- Insomnia treatment is guided by the Delphi consensus recommendations for the management of chronic insomnia in Canada, American Society of Sleep disorders and European Insomnia Disorder guidelines. Before the introduction of orexin antagonists, there was a significant gap in the treatment of CID. Most approved long-term treatments for CID cause significant side effects including physiological or psychological dependance when used long-term and have a negative impact on daytime function, specifically cognitive function.
- Cognitive Behavioral Treatment for insomnia is effective in mild and moderate cases, it is challenging to access and requires time, motivation and commitment; CBT-I may be expensive and time consuming. Conventional treatments for chronic insomnia disorder - hypnotic medications and “Z’ drugs cause sedation, induce tolerance with long term use and can cause withdrawal symptoms. These are not safe to use in the elderly population (high risk of falls and cognitive dysfunction)
- Daridorexant is a first line treatment for Chronic Insomnia disorder as listed in the guidelines for treatment; it has proven safety and efficacy for treatment of CID.

- Current treatments for CID induce sleep by causing sedation and promoting sleep. In contrast, orexin antagonists prevent wakefulness during sleep and thus improve sleep quality and duration, without causing morning sedation and impairment in cognition the following day.
- The most important goals of treatment of CID is to improve sleep at night and daytime function.
- Chronic Insomnia Disorder carries a risk of significant medical and psychiatric co-morbidities, it is one of the major causes of absenteeism from work and accidents. Treatment of CID decrease the incidence of associated co-morbidities. Daridorexant is shown to improve daytime function and reduce the severity of chronic insomnia symptoms.

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

These are the needs that are not being met by currently available treatments for CID:

- Patients may become tolerant to current treatment options
- Not all patients respond to available treatments, given their mechanism of action and limited efficacy
- Current treatments do not lead to improved daytime function
- Treatments are needed that have better efficacy, have better side effect profile, do not cause tolerance and withdrawal and can be safely used in the elderly population, without increased risk for falls
- Treatments are needed that can be used long term, with efficacy that will continue following cessation of treatment. Daridorexant is not associated with rebound insomnia (i.e., insomnia symptoms won't get worse than baseline after treatment cessation). In clinical trials, patients return to placebo levels after the abrupt discontinuation of treatment.
- Treatments should be available and a to broader population

Limitations associated with current treatments

As noted above, current treatments are associated with a multitude of side effects, tolerance, withdrawal, risk of overdose, falls in elderly, impaired cognitive function and sedation during the day.

5. Place in Therapy

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

Mechanism of action

Daridorexant is a medication with a novel mechanism of action that affects the wakefulness system in the brain rather than causing sedation. Other medications, when they are being used inappropriately for long-term in chronic insomnia, could be tapered and discontinued with the addition of this treatment.

Daridorexant addresses the aspect of the disease in a novel way that blocks wakefulness at night

Daridorexant can used as a first line pharmacological treatment for CID (after CBT-I or when CBT-I is not suitable). It can safely be combined with other medications used to treat co-morbidities.

Daridorexant can be used as a first line treatment for all patients with chronic insomnia disorder .

This is a first line pharmacological treatment for CID and other treatments will be recommended only if daridorexant was proven to be ineffective in an individual patient.

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?

Expert consensus recommendations for the management of chronic insomnia in Canada.(*Delphi consensus recommendations for the management of chronic insomnia in Canada,(Charles M. Morin, Atul Khullar, Rebecca Robillard, Alex Desautels, Michael S.B. Mak, Thien Thanh Dang-Vu, Walter Chow, Jeff Habert, Serge Lessard, Lemore Alima, Najib T. Ayas, James MacFarlane, Tetyana Kendzerska, Elliott K. Lee, Colleen E. Carney), Sleep Medicine124, 2024,598-605,ISSN 1389-9457, https://doi.org/10.1016/j.sleep.2024.09.038. https://www.sciencedirect.com/science/arti)* provide answers to the questions above.

Patients in most need for intervention are the ones who are treated with high doses of conventional hypnotics and have developed tolerance and cognitive function impairment. Elderly patients who are in need of a safe medication that will decrease impact of cognition and risk of falls.

Dual orexin antagonists are preferred treatment for Chronic insomnia in all patients, independent of the severity of symptoms and duration. 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).

Detailed clinical history and rating scales for chronic insomnia are necessary for assessment of efficacy of daridorexant over time. Assessment of quality of sleep (using rating scales) and possibly objective sleep assessment such as overnight polysomnography may be added to the assessment tools. Cognitive function tests would further describe the effect of chronic insomnia treatment on cognition, over time.

The diagnosis of CID is clinical diagnosis that can be established using DSM 5 criteria. Insomnia Severity Index is a rating scale often used to support the diagnosis, and assess severity.

Chronic insomnia is commonly an underdiagnosed condition - many individuals minimize their symptoms and ask for help only when they develop medical or psychiatric co-morbidities. Since only a small percentage of people with insomnia disorder will seek medical attention, healthcare providers must be proactive by asking simple screening questions as part of their routine examination, e.g., “Do you have trouble falling or staying asleep?”, “Do you feel refreshed when you wake up in the morning?”, or “Do you feel like your sleep problem interferes with your daytime functioning?”

Effectiveness of the medication across different populations has been demonstrated in clinical practice and confirmed by clinical trials

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?

Use of daridorexant in clinical practice is aligned with the outcomes in clinical trials and effect on daytime function.

Daridorexant trials looked at minimally clinically important differences (MCID) for patients. Those were achieved (among others) for subjective total sleep time (secondary outcome) (60 minutes vs MCID of 55 minutes) and for improvements in the daytime functioning (measured through the IDSIQ scale) for the sleepiness domain (secondary outcome) (-5.7 units vs MCID -4 units). It was also achieved for the IDSIQ scale in general (exploratory outcome) (-19.3 units vs MCID -17). It is reasonable to assume that treatment of chronic insomnia would lead to improved mood and quality of life.

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

Reasons to discontinue daridorexant treatment include lack of effectiveness in certain individuals; infrequent side effects include headaches or morning sedation or increased frequency and severity of nightmares

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]?

There is no need for an assessment from a specialist, Primary care physicians can safely prescribed the medication and assess its effectiveness. It can be safely prescribed in outpatient and community primary care clinics.

6. Additional Information

This is a novel treatment for chronic insomnia that is first line pharmacological treatment, it is safe and effective and could be prescribed for adults and the elderly population.

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 have not received any help to complete 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.

   We have not received any help.

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: Ruzica Jokic
Enter currently held position: Clinical director Mood Disorders Service, Associate Professor, Department of Psychiatry, Queen's University
Date: 19 December 2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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
Esai	x			
Abvie	x			
Indorsia	x			

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

Please note I have provided educational sessions to health care professionals and received honorarium from the above companies.

Declaration for Clinician 2

Name: Dr. Casimiro Cabrera
Position: Mood Disorders Research and Treatment Service, Providence Care Hospital, Kingston, Ontario, Associate Professor, Department of Psychiatry, Queen's University

Date: 19 December 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2. N/A

	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 3

Name: Dr. Gustavo Vasquez
Position: Mood Disorders Research and Treatment Service, Providence Care Hospital, Kingston, Ontario, Professor
Department of Psychiatry, Queen's University
Date: 19/12/2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3. N/A

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

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

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

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0862-000
Generic Drug Name (Brand Name): Daridorexant
Indication: Chronic insomnia disorder
Name of Clinician Group: Synergy Medical Clinic
Author of Submission: Dr. Graham Mansell

1. About Your Clinician Group

Family Physicians

2. Information Gathering

Product Monograph, educational presentations, clinical experience

3. Current Treatments and Treatment Goals

Until the release of dual orexin receptor antagonists, there were no available pharmacologic treatments for chronic insomnia disorder in Canada. It has a novel way of modifying the disease mechanism. Cognitive Behavioral Therapy for insomnia is an effective non-drug treatment, but it is difficult to access and is expensive. Out of necessity, other medications for sleep have been used, but for far beyond the recommended treatment duration of two weeks. Current treatments target symptoms but have risks of habituation and reduced efficacy over time – unlike dual orexin receptor antagonists. An ideal treatment would address chronic insomnia without daytime sedation and improve day time functioning. This would improve symptoms as well as productivity.

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.

Patients become refractory to currently approved treatments. Other treatments are more likely to cause sedation and impair daytime functioning. Better tolerated treatments are required.

5. Place in Therapy

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

The mechanism of action is unique and the treatment would be designed to replace other treatments that have more side effects after 4 weeks of overlapping the prior medications If necessary, the treatment could be paired with other medications. The medication would be a first line medication for chronic insomnia. The drug would cause a shift in the current treatment paradigm. It would not be appropriate to recommend other treatments first for chronic insomnia, because of the side effects and lack of data supporting improved daytime functioning.

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?

Patients with chronic insomnia disorder are most likely to respond. Patients with this disorder experience reduced function and productivity. The are also at risk for other medical conditions and complications such as cardiovascular disease, anxiety, diabetes, obesity, asthma, chronic pain, and depression. The diagnosis is obtained by history and a diagnostic test is not required. Misdiagnosis is unlikely. It is possible that chronic insomnia disorder is underdiagnosed. Ultimately, anyone meeting the diagnostic criteria for chronic insomnia disorder is a candidate to benefit from the treatment

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 practice outcomes are aligned with outcomes in clinical trials. A clinically meaningful response to treatment would be improved sleep and improved daytime functioning. The magnitude of response should not vary among physicians. Patient responses may vary.

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

Some experts recommend treating the patient for a year and then discontinuing the treatment. There does not appear to be any withdrawal symptoms when discontinuing the medication – it is not habit forming. Any adverse effects should prompt a reevaluation of the need for treatment.

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]?

This is a condition that can be diagnosed in the community and treated by family physicians.

6. Additional Information

No additional information fo add.

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.

   No.

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.

   Information on the treatment was presented to clinicians months ago by representatives. Representatives were not consulted in the creation 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: Dr. Graham Mansell
Position: Physician
Date: 11-12-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
Idorsia		x		
Lundbeck		x		
Pfizer Abbvie	x	 x		

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

Declaration for Clinician 2

Name: Dr. Mary Chisholm
Position: Physician
Date: 12-12-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
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 3

Name: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
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 4

Name: <Enter full name>
Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
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 5

Name: <Enter full name>

Position: <Enter currently held position>
Date: <DD-MM-YYYY>

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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**
Add company name				
Add company name				
Add or remove rows as required				

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