

Reimbursement Recommendation

Daridorexant (Quviviq)

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

Sponsor: Idorsia Pharmaceuticals Canada Ltd.

Final recommendation: Do not reimburse

Summary

What Is the Reimbursement Recommendation for Quviviq?

Canada's Drug Agency (CDA-AMC) recommends that Quviviq not be reimbursed by public drug plans for the management of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 2 clinical trials (Study 301 and Study 302) in adults with chronic insomnia disorder (CID) showed that treatment with Quviviq resulted in improvements in the time it takes to fall asleep, the time spent awake after initially falling asleep, and the total sleep duration compared with placebo. However, it was uncertain whether the results were clinically meaningful based on the suggested minimal important differences (MIDs).
- Patients identified a need for treatments that provide consistent, restorative sleep, minimize daytime sedation, and carry a low risk of dependency or cognitive side effects. However, based on the evidence reviewed in the initial meeting and the reconsideration meeting, the Canadian Drug Expert Committee (CDEC) could not determine whether Quviviq meets these needs. The uncertainty was mainly due to a lack of meaningful effect compared to placebo as well as no direct or indirect evidence compared to other treatments used for insomnia.

Additional Information

What Is Insomnia?

Insomnia is a sleep disorder characterized by difficulty falling asleep, staying asleep, and/or getting good quality sleep. Insomnia can also cause feelings of daytime tiredness and affect a person's ability to perform daily activities. CID is a persistent form of insomnia where people regularly have trouble falling or staying asleep 3 times a week for at least 3 months, even when they have enough time and the right conditions to sleep. Globally, about 6% to 15% of adults are affected by insomnia, with roughly 8.8% of adults in Canada affected by CID.

Unmet Needs in Insomnia

There are currently no publicly funded treatments approved in Canada for long-term, continuous use in adults with CID, highlighting a need for treatments with long-term effectiveness that result in uninterrupted and restorative sleep, less stress and anxiety, and improved productivity and

Summary

relationships. There is also a need for safe treatments that have fewer side effects and can be used to manage insomnia without risk of dependency on the medication.

How Much Does Quviviq Cost?

Quviviq is available as 25 mg and 50 mg tablets. At the submitted price of \$2.36 per tablet, both the 25 mg and 50 mg strengths are priced equally. The annual cost of Quviviq is expected to be approximately \$861.99 per patient per year.

Recommendation

CDEC recommends that daridorexant not be reimbursed for the management of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Rationale for the Recommendation

CID is a common condition with many nonpharmacological and pharmacological treatment options available; however, current pharmacological treatment options are used off label, and/or are not intended for long-term use, therefore, CDEC highlighted the unmet therapeutic need in CID for treatment options, specifically in this population. Patient groups emphasized the need for treatments that provide consistent, restorative sleep, minimize daytime sedation, and carry a low risk of dependency or cognitive side effects. CDEC noted that compared to placebo, treatment with daridorexant may meet some of these needs as it resulted in improvement in relevant clinical outcomes such as sleep maintenance, onset, duration, and quality; however, the magnitude of the benefit was uncertain and CDEC could not substantiate that daridorexant meets these needs relative to other treatment options.

Evidence from 2 double-blind, placebo-controlled trials (Study 301 and Study 302) evaluating the efficacy and safety of daridorexant compared to placebo in adult patients with CID, demonstrated that treatment with daridorexant 50 mg and 25 mg resulted in a statistically significant reduction (improvement) in sleep maintenance (mean wake after sleep onset [WASO]), sleep onset (mean latency to persistent sleep [LPS]), and increase in sleep duration (mean subjective total sleep time [sTST]) at 1 and 3 months compared with placebo. However, CDEC noted that it was uncertain whether the results for these outcomes were clinically meaningful based on the suggested MIDs identified in the clinical report, the high placebo response rate, as well as confidence intervals (CIs) which included the possibility of no clinically meaningful benefit. CDEC also noted that there were improvements in mean Insomnia Severity Index (ISI) total scores and Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) total scores from baseline to month 1 and month 3 in all treatment groups in both trials. However, these outcomes were exploratory and were not controlled for multiplicity. Additionally, the clinical relevance of these measures remains uncertain due to their subjective nature, their limited applicability in clinical practice, and lack of clarity on whether the results were clinically meaningful.

No direct or indirect comparative evidence between daridorexant and other treatments for CID was included in the submission; therefore, the comparative efficacy and safety of daridorexant versus pharmacological and nonpharmacological treatments used in Canada remains unknown and is a significant limitation of the evidence.

Discussion Points

- **Request for reconsideration from the sponsor:** The sponsor requested a reconsideration of the initial draft recommendation to not reimburse daridorexant for insomnia. There were 6 issues outlined by the sponsor in the request for reconsideration that were discussed by CDEC: the inappropriateness of pharmacological comparators in CID, undervaluation of subjective outcomes in insomnia, reliance on expert-derived MIDs rather than validated patient-reported outcome MIDs, the misinterpretation of MIDs and CIs undermining the meaningfulness of results, the lack of comparative data with pharmacological comparators beyond 1 month, and the recognized safety advantage of daridorexant which contradicts the demand for comparative efficacy evidence.
- **Unmet need:** CDEC considered the needs identified by patients which included treatments that provide consistent and restorative sleep, minimize daytime sedation, and carry a low risk of dependency or cognitive side effects. CDEC recognized the reimbursement request for the drug under review was for chronic insomnia, which was narrower than the Health Canada indication and aligned with the evidence submitted. CDEC discussed that there is currently no publicly funded treatment approved in Canada for long-term, continuous use in CID, highlighting an unmet therapeutic need. Additionally, CDEC acknowledged the health equity concerns in CID given the predominantly female population and challenges in accessing some therapeutic options (e.g., cognitive-behavioural therapy for insomnia [CBT-I]). CDEC noted that the pivotal evidence for daridorexant (Study 301 and Study 302) may meet some patient needs (i.e., improved sleep maintenance, sleep onset, and sleep duration) compared to placebo; however, the clinical significance of effects was uncertain as the CIs included the possibility of no meaningful benefit. Furthermore, CDEC was unable to ascertain whether daridorexant meets the unmet needs identified versus currently available active treatments, which was consequential given the importance of reduced next-day residual effects (e.g., grogginess, sedation) that occur with currently used, off-label treatments. CDEC noted that with a terminal half-life of approximately 8 hours, it is expected that daridorexant would not affect daytime functioning and may reduce or eliminate grogginess, and the pivotal studies suggested improvements in self-reported morning sleepiness. However, given the limitations of evidence, particularly around the clinical meaningfulness of findings, generalizability of results, and the challenges in evaluating perceived improvements in sleep, as well as the lack of comparative evidence versus relevant treatments, CDEC was unable to conclude whether daridorexant meets these needs. These needs were also discussed at the reconsideration meeting and CDEC upheld their initial conclusion. CDEC also heard from the clinical experts consulted for this review that based on their experience, there is a population of patients with CID that might benefit from daridorexant. However, based on the evidence reviewed and the variability across individuals, CDEC could not define the specific population who would receive the most benefit from this treatment.
- **Patient and clinician group feedback on the draft recommendation:** During the reconsideration meeting, CDEC reviewed feedback on the draft recommendation from 2 patient groups and 9 clinician groups. This feedback emphasized and noted that CDEC did not sufficiently consider

in their initial assessment the significant unmet need and potential ethical conflict for therapies that safely manage chronic insomnia, for which there are no alternative pharmacological options indicated; CDEC did not give sufficient weight to the demonstrated efficacy of daridorexant or the value of patient-reported outcomes; and the superior safety of daridorexant compared to alternative pharmacological treatments that are used off label (benzodiazepines, antidepressants, serotonin receptor antagonists). During the reconsideration meeting, CDEC recognized the patient considerations on the ethical issues surrounding off-label treatment options, as well as the collective perspectives and experiences of the clinician groups and individual clinicians who treat patients with insomnia particularly with respect to the disinclination of prescribing short-term therapies for a chronic condition, as well as the generally accepted perception of improved safety with daridorexant. Furthermore, as previously indicated, CDEC acknowledged the unmet therapeutic need in CID. However, CDEC could not establish that the available evidence adequately substantiates that daridorexant meets the identified needs given the limitations identified in the evidence reviewed; and modest magnitude of benefit compared to placebo.

- Relevant comparator and place in therapy:** CDEC discussed the place in therapy of daridorexant for the treatment of CID and noted that it can be used as either first-line or second-line treatment as a pharmacological alternative to first-line CBT-I, when CBT-I is inappropriate, unavailable, or has failed. CDEC noted the lack of accessibility, or knowledge of, CBT-I in Canada. During the initial and reconsideration meetings, CDEC discussed the current treatment landscape for insomnia, noting that for CID, all funded pharmacological treatments are used off label (e.g., Z-drugs, benzodiazepines, gamma-aminobutyric acid [GABA] agonists). CDEC also discussed the clinical equipoise in CID where the sponsor, patient groups, and clinician groups emphasized that evaluating the long-term effects of these therapies would be unethical. CDEC reiterated that patients with CID currently receive these treatments, whether appropriate or not, are therefore relevant comparators in this setting. During the initial deliberation, the clinical experts mentioned that several network meta-analyses have been published comparing daridorexant with other treatments for the management of acute and long-term insomnia. However, CDEC noted that no direct or indirect comparative evidence evaluating the efficacy and safety of daridorexant relative to other available nonpharmacological and pharmacological options for the treatment of CID was submitted by the sponsor, despite these comparators being widely used in clinical practice in Canada. During the reconsideration meeting, CDEC acknowledged the difficulty in conducting robust indirect analyses given the lack of long-term evidence available for off-label treatments in the chronic setting. Regardless, CDEC was unable to conclude that daridorexant results in any improvement in insomnia outcomes versus relevant comparators, which also precludes any assessment of the most appropriate place in therapy.
- Certainty of evidence and relevance of outcomes:** CDEC discussed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of selected outcomes from Study 301. CDEC noted that at 3 months, the least-squares mean (LSM) difference in change from baseline in sleep maintenance measured by WASO (LSM = -18.30 minutes; 95% CI, -24.76 minutes to -11.85 minutes), onset measured by LPS (LSM = -11.67 minutes; 95% CI, -17.03 minutes to -6.32 minutes), and duration measured by sTST (LSM = 19.77 minutes; 95% CI,

9.30 minutes to 30.24 minutes) were associated with improvements relative to placebo; however, the committee emphasized that the clinical meaningfulness between daridorexant and placebo was unclear based on the between-group MIDs provided, and in discussion with the clinical experts. However, CDEC noted that when considering the within-group MIDs for subjective outcomes of sTST, IDSIQ, and ISI — which they noted were more important to individual patients — results for the daridorexant 50 mg group in Study 301 had the potential to be clinically meaningful but were associated with imprecision. CDEC and the clinical experts highlighted that primary outcomes in the studies (WASO and LPS) were measured using sleep studies (polysomnography), although providing an objective measure of sleep, are not used in clinical practice to diagnose and assess patients with CID in Canada. Conversely, CDEC noted that secondary outcomes (e.g., sTST and IDSIQ) were measured using subjective tools; however, as noted, the clinical meaningfulness of these results was uncertain based on point estimates not reaching the between-group MIDs, subjectivity in assessments, and high placebo response, as well as the novelty and limited application of assessment tools in clinical practice (i.e., IDSIQ and ISI). During the reconsideration meeting, CDEC heard from the clinical experts that the between-group MIDs considered in the review were potentially too high; however, CDEC noted that in the absence of alternative between-group estimates for clinical importance, the published MIDs were considered. CDEC also noted several limitations in the included studies that restricted the generalizability of results to real-world clinical practice, such as a high proportion of screening failures, and the exclusion of patients with comorbid psychiatric disorders and those using other central nervous system-active medications.

- **Adverse effects:** Patients highlighted the need for treatments that carry a low risk of dependency or cognitive side effects, which are common with currently used, off-label pharmacotherapies (e.g., benzodiazepines). During the initial and reconsideration meetings, CDEC discussed the safety profile of daridorexant from the pivotal studies, agreeing with the clinical experts that daridorexant has an acceptable and manageable safety profile that suggests that there were no adverse effects (AEs) indicative of potential abuse (apart from accidental overdose occurring in 2.6% or fewer patients in any treatment group in the pivotal trials), and there were no safety concerns regarding rebound insomnia, next-morning residual effects, or suicidality. CDEC also noted that there was no evidence of withdrawal symptoms upon discontinuation of treatment with daridorexant in Study 303 based on results from the Benzodiazepine Withdrawal Symptom Questionnaire. During the reconsideration meeting, CDEC upheld their initial conclusion, noting that these alternative treatments have their limitations, undesirable AEs, and tolerance issues. CDEC further emphasized that although there is a perceived safety benefit of daridorexant given the mechanism of action, and based on the general experiences from clinicians, no comparative evidence was provided validating the theoretical safety advantages that daridorexant offers.
- **Supportive evidence:** CDEC discussed the results from 1 long-term extension (LTE) study (Study 303), which showed that changes in subjective wake after sleep onset (sWASO), subjective latency to persistent sleep onset (sLSO), and sTST were maintained over time for patients continuing treatment with either 25 mg or 50 mg daridorexant; however, there were important methodological and statistical limitations of this study, and based on the suggested MIDs for these outcomes and wide

CIs, the results do not represent clinically meaningful improvements. Furthermore, CDEC noted that the results may be overestimated based on the dropout rate and likely responder bias and therefore may not be generalizable to the population of patients with CID in Canada.

Background

Insomnia is characterized by persistent sleep difficulty despite adequate sleep opportunity and associated daytime dysfunction. Patients with insomnia experience dissatisfaction with their sleep quality or duration due to difficulties with initiating or maintaining sleep or waking up too early. For a diagnosis of CID — as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*, which refers to it as an insomnia disorder — symptoms must occur at least 3 times per week for at least 3 months and be present despite adequate conditions for sleep. It must also be associated with significant distress or impairment of daytime functioning, and impairment in social, occupational, academic, behavioural, or other important areas of functioning. The etiology of insomnia includes a combination of predisposing factors which increase the risk for CID (e.g., chronic mental health or neurological conditions), precipitating events that lead to sleep disruption (e.g., severe accident leading to physical injury, death of a close family member, or change in occupation), and perpetuating factors which consist of behavioural and cognitive compensatory responses to sleeplessness which may contribute to persistent physiologic arousal contributing to the continuation of insomnia (e.g., worry about sleep loss or clock watching in bed).

A range of risk factors have been implicated in the development of insomnia including older age, family history of insomnia, and female sex. Insomnia often coexists with psychiatric disorders (e.g., anxiety, depression, or bipolar disorder), medical conditions (e.g., pulmonary disease, diabetes, or cancer), and neurological conditions (e.g., epilepsy, dementias, or multiple sclerosis). CID has a negative impact on patients' daytime functioning, safety, and quality of life. Patients with CID report increased fatigue, confusion, tension, anxiety, and depression. Patients tend to overestimate the magnitude of their performance deficits as well as the magnitude of their sleep deficits. Nevertheless, insomnia has been associated with decreased work productivity, increased health care utilization, and risk of accidents. Patients with CID frequently seek over-the-counter remedies and have an increased risk of developing substance use disorders. When untreated, symptoms of insomnia can exacerbate existing health issues and lead to new physical and mental health complications over time, including cardiovascular, psychiatric, and neurological conditions. Both CID and decreased total sleep time are independent risk factors for suicidal ideation and behaviour. There are a wide range of prevalence estimates for insomnia due to variances in case definitions, assessment procedures, sample characteristics, and length of assessments. In general, approximately 30% of adults report experiencing insomnia symptoms of any severity at some point in their lives, with around 10% to 15% also experiencing daytime consequences such as fatigue. When using more stringent *Diagnostic and Statistical Manual of Mental Disorders (DSM)* or *International Classification of Sleep Disorders* diagnostic criteria, CID prevalence rates tend to cluster between 6% and 10%. A 2023 RAND Europe report estimated that the global prevalence of CID in the general adult population ranges from 6% to 14.8% based on

data from 7 studies comprising 6 countries in Europe, the UK, and the US. The report estimated that the prevalence of CID in the general adult population in Canada was 8.8% (95% CI, 5.6% to 12.0%).

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 2 phase III, double-blind, placebo-controlled randomized controlled trials (RCTs) in adult patients with moderate to severe CID based on DSM-5 criteria included in the systematic review section and 1 LTE study
- patients' perspectives gathered by 4 patient groups: Gastrointestinal Society, Menopause Chicks, Mood Disorders Society of Canada, and Migraine Canada, and from a group of 8 adults in Canada living with CID representing a range of patient groups
- input from public drug plans that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with CID
- input from 12 clinician groups: Mood Disorders Research and Treatment Service, the Family Physician Airways Group of Canada, the Canadian Consortium of Sleep and Sleep Interested Physicians, the Synergy Medical Clinic, MedSleep, as well as submissions from psychiatrists in British Columbia and Quebec, family physicians, a neurologist, and an inpatient mental health pharmacist
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the sponsor's request for reconsideration (described subsequently)
- feedback on the draft recommendation.

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided to CDA-AMC by the patient and clinician groups who responded to our call for input and from clinical experts consulted by for the purpose of this review.

Patient Input

CDA-AMC received patient input from 4 groups, including the Gastrointestinal Society, who used information from meetings with health care experts and researchers, as well as results from surveys conducted on digestive and liver diseases and disorders; Menopause Chicks, who surveyed women aged 45 to 64 years experiencing sleep disruptions; a submission from a group of 8 adults in Canada living with CID representing a range of patient groups; and a joint submission from Mood Disorders Society of Canada (MDSC) and Migraine Canada, who surveyed and interviewed patients with insomnia, including 1 patient with experience with the treatment under review.

The input from the Gastrointestinal Society noted that CID is an independent condition that is also closely linked to a range of comorbidities, including cardiovascular disease, diabetes, obesity, cancer, and gastrointestinal diseases. In the survey conducted by Menopause Chicks, more than 85% of patients surveyed believe the underlying cause of their insomnia was due to hormone changes. The input from adults in Canada living with CID stated that the negative effects of CID are often underestimated, with significant impacts on the daily life of those affected with symptoms including persistent fatigue, difficulty concentrating, physical discomfort such as joint pain and muscle soreness, pervasive lack of energy that impedes self-care and routines (i.e., exercise, maintaining household responsibilities, and childcare), emotional strain (feelings of frustration and anxiety), and social isolation due to exhaustion. Patients expressed that those around them often do not understand their struggles, adding to feelings of isolation. The input noted that patients' sleep difficulties exacerbate other health conditions like migraines and depression and patients often miss time at work, school, or volunteering due to their symptoms. The Gastrointestinal Society noted that beyond the workplace, insufficient sleep can affect an individual's emotional well-being, behaviour, and interactions, contributing to memory lapses, accidents, injuries, and mood disturbances. Input from patients from the MDSC and Migraine Canada submission reported concerns about the long-term impacts of CID on their mental and physical health. The input also noted that partners and family members often endure sleepless nights alongside their loved ones, leading to stress, frustration, and relationship strain.

Pharmacological treatments that patients have used include sedatives or hypnotics, GABA agonists, antidepressants, antipsychotics, dual orexin receptor antagonists (DORAs) (e.g., lemborexant), and cannabinoids. Input from Menopause Chicks noted that most patients surveyed were prescribed selective serotonin reuptake inhibitors as a sleep aid. The input from adults in Canada living with CID, and the input received from the MDSC and Migraine Canada submission highlighted that patients also try nonpharmaceutical options including lifestyle adjustments, strict sleep routines, meditation, and exercise. Due to high unmet needs, some patients also take over-the-counter supplements and drugs such as antihistamines, melatonin, magnesium, L-theanine, herbal products (chamomile, lavender, valerian root, and so forth), and antihistamines (diphenhydramine), among others. Patients reported that these treatment options provided short-term relief, relaxation, and minor sleep support. Drawbacks included grogginess, impaired functioning, inconsistent results with continued persistent daily fatigue, and high costs. Across inputs, many patients expressed fear of dependency on medicated sleep aids and concerns about long-term side effects, including potential cognitive impacts. However, patients across submissions noted that currently available treatment options do not address the core issue of achieving deep, restorative sleep.

As such, patient groups emphasized the need for treatments that offer consistent and restorative sleep, reduced or eliminated grogginess, and a low risk of dependency or cognitive side effects. Patients noted that addressing these unmet needs could reduce the physical, emotional, and financial strains as well as offer a better quality of life through improved sleep and daily functioning. Among the 1 patient with experience with daridorexant from the MDSC and Migraine Canada input, caregivers reported an improvement in the patient's ability to fall asleep and stay asleep without any outward signs of next-day side effects.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts consulted by CDA-AMC for this review noted that, because of the multifactorial nature of CID and its frequent comorbidities, it is important to have a variety of pharmacological and nonpharmacological approaches in addition to CBT-I. The experts agreed that there is a need for targeted therapies to address the multiple factors that contribute to insomnia (e.g., physiologic, biologic, circadian, and psychiatric) that are associated with long-term efficacy, improved tolerance, and fewer AEs to improve compliance.

The experts noted that daridorexant may be a first-line pharmacological therapy for insomnia disorder if CBT-I is not helpful or not possible. However, the experts noted that deprescribing the traditional sedative-hypnotics poses a challenge as patients often prefer current treatment options due to their rapid onset of action. As such, transitioning to daridorexant may be difficult as DORAs may take 4 to 8 weeks to demonstrate results.

Per the clinical experts, patients with CID, especially those who may have significant functional impairment would benefit the most from new treatments such as daridorexant, while other drugs might be more appropriate for patients with comorbid conditions such as chronic pain or depression. Experts suggested using DORAs preferentially in patients where minimizing AEs is a priority, given their favourable side effect profile. Narcolepsy would be an absolute contraindication for DORAs.

The clinical experts mentioned that the response to treatment is usually assessed by patients' impression of improvement in sleep quality, quantity, and daytime functioning, and other symptoms. They noted that each patient will likely have their own subjective standard of what they would define as adequate benefit from treatment. The clinical experts also noted that optimal treatment response with daridorexant may not be observed until 8 weeks of treatment. As such, patients may choose to discontinue treatment due lack of efficacy. AEs (e.g., hallucinations, vivid disturbing dreams, and suicidality) that outweigh any potential benefits are also potential reasons to discontinue treatment.

Clinician Group Input

Twelve clinician groups provided input for this review, all of whom have work experience with patients with CID. These included the Mood Disorders Research and Treatment Service, the Family Physician Airways Group of Canada, the Canadian Consortium of Sleep and Sleep Interested Physicians, the Synergy Medical Clinic, MedSleep, as well as submissions from psychiatrists in British Columbia and Quebec, family physicians, a neurologist, and an inpatient mental health pharmacist. The input stated that current treatment options for insomnia include nonpharmacological therapies such as sleep hygiene and CBT-I which they also noted can be costly and has limited availability in Canada. The input stated that pharmacological options, particularly GABA agonists, are only prescribed for short-term use, are limited by poor efficacy and next-day sedation, often require dose escalation, can lead to dependence or nonresponse, can lead to withdrawal symptoms upon discontinuation, are associated with cognitive side effects, and there is limited or no clinical data supporting their use for CID. As such, to improve patient outcomes, the clinician groups noted that there is a need for treatments that improve daytime function, are tolerable, affordable, and safe.

The clinician groups stated that daridorexant also highlighted the unique mechanism of action of daridorexant which reduces wakefulness without causing sedation. Daridorexant would be used first-line for CID after CBT-I or when CBT-I is not suitable, according to the input. With regards to assessing response to treatment, the clinician groups noted that given the prevalence of insomnia in Canada and limited resources, frequent polysomnograms are not practical for use in clinical practice. Some of the clinician groups highlighted the use of the ISI screening tool and other patient-reported outcomes used in research to assess treatment response; however, the clinical experts consulted for this review noted the ISI tool may be less commonly used in clinical practice in Canada. The clinician groups noted that a clinically meaningful response to treatment includes improved next-day functioning, improved duration and quality of sleep, and a reduction in ISI. Potential reasons for discontinuing treatment include side effects such as reduced daytime functioning, nightmares, or sleep paralysis. Various clinicians agreed that daridorexant would be particularly suitable for patients at risk for drug dependence or addiction and for older patients given the unsuitability of many other drugs because of the potential for cognitive impairment and fall risk. Clinician groups agreed with the clinical experts consulted for this review that daridorexant would likely be prescribed by primary care physicians in outpatient settings and no specific dependence or rebound issues would need to be addressed for patients to discontinue daridorexant.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for daridorexant:

- considerations for relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- care provision issues.

Clinical Evidence

Systematic Review

Description of Studies

Two phase III, double-blind, placebo-controlled RCTs, Study 301 (N = 930) and Study 302 (N = 617), were included in this review. Both studies aimed to assess the efficacy and safety of daridorexant (50 mg and 25 mg in Study 301, and 25 mg in Study 302) in adult patients with CID after month 1 and month 3 of treatment. The primary outcome in the included trials was change from baseline in sleep maintenance (WASO) and sleep onset (LPS), measured objectively via polysomnography (PSG). Other outcomes relevant to this

review were change from baseline in sleep duration (sTST), sleep quality, daytime functioning, ISI score, total sleep time for each sleep stage, and safety.

Both studies enrolled adult patients with moderate to severe CID based on *DSM-5* criteria. Patients with specific comorbid conditions were excluded, such as those with acute or unstable psychiatric conditions, suicidal ideation with intent, alcohol or drug addiction, any lifetime history of suicide attempt, sleep-related breathing disorders, or narcolepsy. Patients who were unable or unwilling to discontinue concomitant use of moderate CYP3A4 inhibitors were also excluded from the trials. The baseline characteristics of the patients enrolled in both studies were generally similar across the treatment groups, with a mean age of 55.1 years (standard deviation [SD] = 15.4 years) to 56.7 years (SD = 14.1 years) across the studies. Most patients identified as white (86.7% to 92.6%), with 6% to 9.7% who identified as Black or African American, and 0.6% to 3.6% of patients who identified as Asian. In both studies, CBT-I was rarely used by the patients, with only 3 patients in Study 301 having received CBT-I at screening.

Efficacy Results

Sleep Maintenance

Sleep maintenance reported as change from baseline in WASO was 1 of the primary outcomes in Study 301 and Study 302. In Study 301, the mean WASO at baseline was 95.48 minutes (SD = 37.81 minutes) in the daridorexant 50 mg group, 97.87 minutes (SD = 38.77 minutes) in the daridorexant 25 mg group, and 102.51 minutes (SD = 40.77 minutes) in the placebo group. At month 1, the least squares (LS) mean change from baseline in WASO was –28.98 minutes (95% CI, –32.67 minutes to –25.30 minutes), –18.40 minutes (95% CI, –22.13 minutes to –14.67 minutes), and –6.20 minutes (95% CI, –9.93 minutes to –2.48 minutes), in the daridorexant 50 mg, daridorexant 25 mg, and placebo groups, respectively. The LS mean difference in change from baseline in WASO at 1 month compared to placebo was –22.78 minutes (97.5% CI, –28.75 minutes to –16.82 minutes) and –12.20 minutes (97.5% CI, –18.19 minutes to –6.21 minutes), in favour of daridorexant 50 mg and 25 mg, respectively. At month 3, the LS mean change from baseline was –29.41 minutes (95% CI, –33.40 minutes to –25.43 minutes) in the daridorexant 50 mg group, –22.97 minutes (95% CI, –26.96 minutes to –18.99 minutes) in the daridorexant 25 mg group, and –11.11 minutes (95% CI, –15.13 minutes to –7.09 minutes) in the placebo group. The LS mean difference in change from baseline in WASO compared to placebo was –18.3 minutes (97.5% CI, –24.76 minutes to –11.85 minutes) and –11.86 minutes (97.5% CI, –18.30 minutes to –5.42 minutes) in favour of daridorexant 50 mg and 25 mg, respectively.

In Study 302, the mean WASO at baseline was 106.31 minutes (SD = 49.10 minutes) in the daridorexant 25 mg group and 108.07 minutes (SD = 48.71 minutes) in the placebo group. At month 1, the LS mean change from baseline was –24.19 minutes (95% CI, –28.47 minutes to –19.91 minutes) for daridorexant 25 mg and –12.57 minutes (95% CI, –16.82 minutes to –8.32 minutes) for placebo, corresponding to an LS mean difference of –11.62 minutes (95% CI, –17.60 minutes to –5.63 minutes) in favour of daridorexant 25 mg. Results of the subgroup analysis showed that in male patients, there were no difference between groups (mean difference = 3.94, 95% CI, –13.58 to 5.69). At month 3, the LS mean change from baseline in the daridorexant 25 mg group was –24.25 minutes (95% CI, –29.02 minutes to –19.47 minutes) and

–10.25 minutes (95% CI, –16.95 minutes to –3.55 minutes) in the placebo group, representing an LS mean difference of –14.00 minutes (–18.76 minutes to –9.24 minutes), in favour of daridorexant 25 mg.

Sleep Onset

Sleep onset reported as change from baseline in LPS was 1 of the primary outcomes in Study 301 and Study 302. In Study 301, the mean LPS at baseline was 63.62 minutes (SD = 37.39 minutes) in the daridorexant 50 mg group, 67.27 minutes (SD = 38.56 minutes) in the daridorexant 25 mg group, and 66.54 minutes (SD = 39.77 minutes) in the placebo group. At month 1, the LS mean change from baseline in LPS was –31.20 minutes (95% CI, –34.51 minutes to –27.90 minutes), –28.17 minutes (95% CI, –31.51 minutes to –24.83 minutes), and –19.85 minutes (95% CI, –23.18 minutes to –16.52 minutes) in the daridorexant 50 mg, daridorexant 25 mg, and placebo groups, respectively. The LS mean difference in change from baseline in LPS at month 1 compared to placebo was –11.35 minutes (97.5% CI, –16.694 minutes to –6.015 minutes) and –8.32 minutes (97.5% CI, –13.69 minutes to –2.96 minutes), in favour of daridorexant 50 mg and 25 mg, respectively. At month 3, the LS mean change from baseline in LPS was –34.80 minutes (95% CI, –38.12 minutes to –31.49 minutes), –30.73 minutes (95% CI, –34.04 minutes to –27.41 minutes), and –23.13 minutes (95% CI, –26.46 minutes to –19.80 minutes) in the daridorexant 50 mg, daridorexant 25 mg, and placebo groups, respectively. The LS mean difference in change from baseline in LPS at month 3 compared to placebo was –11.67 minutes (97.5% CI, –17.03 minutes to –6.32 minutes) and was –7.59 minutes (97.5% CI, –12.94 minutes to –2.25 minutes) in favour of daridorexant 50 mg and 25 mg, respectively.

In Study 302, the mean LPS at baseline were 68.88 minutes (SD = 40.55 minutes) in the daridorexant 25 mg group and 71.82 minutes (SD = 46.09 minutes) in the placebo group. At month 1, the LS mean change from baseline was –26.46 minutes (95% CI, –30.63 minutes to –22.29 minutes) for daridorexant 25 mg and –20.01 minutes (95% CI, –24.15 minutes to –15.88 minutes) for placebo, corresponding to an LS mean difference of –6.45 minutes (95% CI, 12.28 minutes to –0.61 minutes) in favour of daridorexant 25 mg. At month 3, the LS mean change from baseline in the daridorexant 25 mg group was –28.91 minutes (95% CI, –33.41 minutes to –24.40 minutes) and –19.89 minutes (95% CI, –24.38 minutes to –15.41 minutes) in the placebo group, representing an LS mean difference of –9.01 minutes (95% CI, –15.34 minutes to –2.68 minutes), in favour of daridorexant 25 mg.

Sleep Duration

Sleep duration, measured subjectively, was reported as change from baseline in sTST and was a secondary outcome in Study 301 and Study 302.

In Study 301, the mean sTST at baseline was 313.18 minutes (SD = 57.60 minutes) in the daridorexant 50 mg group, 309.85 minutes (SD = 60.11 minutes) in the daridorexant 25 mg group, and 315.89 minutes (SD = 53.14 minutes) in the placebo group. At month 1, the LS mean change from baseline in subjective TST was 43.62 minutes (95% CI, 38.17 minutes to 49.06 minutes), 34.18 minutes (95% CI, 28.72 minutes to 39.65 minutes), and 21.56 minutes (95% CI, 16.10 minutes to 27.02 minutes) in the daridorexant 50 mg, daridorexant 25 mg, and placebo groups, respectively. The LS mean difference in change from baseline in sTST at month 1 compared to placebo was 22.06 minutes (97.5% CI, 13.30 minutes to 30.18 minutes) and 12.62 minutes (97.5% CI, 3.85 minutes to 21.39 minutes), in favour of daridorexant 50 mg and 25 mg,

respectively. At month 3, the LS mean change from baseline was 57.67 minutes (95% CI, 51.17 minutes to 64.17 minutes) in the daridorexant 50 mg group, 47.83 minutes (95% CI, 41.33 minutes to 54.33 minutes) in the daridorexant 25 mg group, and 37.90 minutes (95% CI, 31.39 minutes to 44.40 minutes) in the placebo group, representing an LS mean difference of 19.77 minutes (97.5% CI, 9.30 minutes to 30.24 minutes) and 9.93 minutes (97.5% CI, -0.54 minutes to 20.40 minutes), in favour of daridorexant 50 mg and 25 mg, respectively.

In Study 302, the mean sTST at baseline were 308.49 minutes (SD = 52.85 minutes) in the daridorexant 25 mg group and 307.57 minutes (SD = 51.52 minutes) in the placebo group. At month 1, the LS mean change from baseline in sTST was 43.77 minutes (95% CI, 38.14 minutes to 49.41 minutes) in the daridorexant 25 mg group, and 27.64 minutes (95% CI, 22.02 minutes to 33.27 minutes) in the placebo group. The mean change from baseline in sTST with daridorexant 25 mg was 16.13 minutes longer than that with placebo (95% CI, 8.22 minutes to 24.04 minutes). At month 3, the LS mean change from baseline in sTST was 56.18 minutes (95% CI, 49.81 minutes to 62.55 minutes) in the daridorexant 25 mg group and 37.12 minutes (95% CI, 30.78 minutes to 43.46 minutes) in the placebo group, representing an LS mean difference of 19.06 minutes (95% CI, 10.13 minutes to 27.99 minutes), in favour of daridorexant 25 mg.

Sleep Quality

Sleep quality was determined by Sleep Diary Questionnaire (SDQ) and was considered as an exploratory outcome in the included studies. In Study 301, the mean visual analogue scale (VAS) score for sleep quality at baseline was 36.23 (SD = 17.03) in the daridorexant 50 mg group, 35.56 (SD = 17.77) in the daridorexant 25 mg group, and 35.60 (SD = 17.78) in the placebo group. At month 1, the mean changes from baseline at month 1 were 14.21 points (SD = 18.95 points), 11.35 points (SD = 15.65 points), and 7.04 points (SD = 13.74 points) for the daridorexant 50 mg, daridorexant 25 mg, and placebo groups, respectively. At month 3, the mean changes from baseline were 20.21 points (SD = 22.15 points) for the daridorexant 50 mg group, 18.20 points (SD = 19.10 points) for the daridorexant 25 mg group, and 13.95 points (SD = 18.85 points) for the placebo group.

In Study 302, the mean VAS sleep quality score at baseline was 37.94 (SD = 15.02) in the daridorexant 25 mg group, and 36.91 (SD = 14.77) in the placebo group. At month 1, the mean changes from baseline in the daridorexant 25 mg group was 11.20 points (SD = 15.55 points) and in the placebo group was 9.41 points (SD = 14.44 points). At month 3, the mean changes from baseline in the daridorexant 25 mg group was 17.77 points (SD = 18.55 points) and that in the placebo group was 13.18 points (SD = 17.33 points).

Change From Baseline in IDSIQ Total Score

In Study 301, the mean IDSIQ total scores at baseline were 74.52 points (SD = 25.16 points), 73.06 points (SD = 24.55 points), and 73.55 points (SD = 24.64 points) in the daridorexant 50 mg, daridorexant 25 mg, and placebo groups. The LS mean difference in change from baseline in IDSIQ total score compared to placebo at month 1 was -7.24 points (95% CI, -9.785 points to -4.698 points) and -2.94 points (95% CI, -5.487 points to -0.385 points) in favour of daridorexant 50 mg and daridorexant 25 mg, respectively. The LS mean difference between groups at month 3 compared to placebo were -7.20 points (95% CI, -10.544

points to –3.862 points), and –3.46 points (95% CI, –6.809 points to –0.113 points), in favour of daridorexant 50 mg and daridorexant 25 mg, respectively.

In Study 302, the mean IDSIQ total scores at baseline were 73.14 points (SD = 21.21 points) in the daridorexant 25 mg group, and 74.48 points (SD = 20.26 points) in the placebo group. At month 1, compared to placebo, the mean difference from baseline in the daridorexant 25 mg group was 3.11 points (95% CI, –5.807 points to –0.412 points) lower in favour of daridorexant. At month 3, there was a decrease in IDSIQ total score of 4.23 points (95% CI, –7.477 points to –0.986 points) compared to placebo in favour of daridorexant 25 mg.

Change From Baseline in ISI Score

The change from baseline in ISI score was an exploratory outcome in the included trials. In Study 301, the mean ISI score at baseline was 19.3 points (SD = 4.0 points) in the daridorexant 50 mg group, 19.0 points (SD = 4.3 points) in the daridorexant 25 mg group, and 19.2 points (SD = 4.0 points) in the placebo group. At month 1, the LSM change from baseline was –4.81 points (95% CI, –5.36 points to –4.26 points), –4.07 points (95% CI, –4.63 points to –3.51 points), and –3.05 points (95% CI, –3.60 points to –2.50 points) in the daridorexant 50 mg group, daridorexant 25 mg group, and in the placebo group, respectively. Compared to placebo, there was a decrease in ISI score of –1.76 points (95% CI, –2.54 points to –0.99 points) in the daridorexant 50 mg group and –1.02 points (95% CI, –1.80 points to –0.24 points) in the daridorexant 25 mg group. At month 3, the LSM change from baseline was –7.17 points (95% CI, –7.84 points to –6.50 points), –6.02 points (95% CI, –6.69 points to –5.35 points), –5.19 points (95% CI, –5.86 points to –4.52 points) in the daridorexant 50 mg group, daridorexant 25 mg group, and in the placebo group, respectively. Compared to placebo, there was a decrease in ISI score of –1.98 points (95% CI, –2.92 points to –1.04 points) in the daridorexant 50 mg group and –0.83 points (95% CI, –1.78 points to 0.11 points) in the daridorexant 25 mg group.

In Study 302, the mean ISI score at baseline was 19.5 points (SD = 4.0 points) in the daridorexant 25 mg group, and 19.6 points (SD = 4.1 points) in the placebo group. At month 1, the mean changes from baseline in the daridorexant 25 mg group was –5.1 points (SD = 5.2 points) and in the placebo group was –3.8 points (SD = 4.6 points). At month 3, the mean changes from baseline in the daridorexant 25 mg group was –6.9 points (SD = 6.0 points) and in the placebo group was –5.4 points (SD = 5.5 points).

Change From Baseline in Duration of TST in Each Sleep Stage

The change from baseline for the duration of TST in each sleep stage (i.e., stage 1, stage 2, slow-wave sleep [SWS], and rapid eye movement [REM]) was an exploratory end point in the included trials.

In Study 301, the change from baseline in stage 1 to month 1 for daridorexant 50 mg, daridorexant 25 mg, and placebo was 5.41 minutes, 4.26 minutes, and 2.59 minutes, respectively. For stage 2, the change from baseline to month 1 for daridorexant 50 mg, daridorexant 25 mg, and placebo was 34.74 minutes, 29.79 minutes, and 16.10 minutes, respectively. For SWS, the change from baseline to month 1 for daridorexant 50 mg, daridorexant 25 mg, and placebo was 2.16 minutes, 0.71 minutes, and 1.60 minutes, respectively. For REM, the change from baseline to 1 month for daridorexant 50 mg, daridorexant 25 mg, and placebo

was 15.51 minutes, 13.50 minutes, and 9.22 minutes, respectively. The change from baseline to month 3 in the daridorexant 50 mg, daridorexant 25 mg, and placebo groups were 6.89 minutes, 5.67 minutes, and 4.51 minutes for stage 1; 37.69 minutes, 36.19 minutes, and 25.07 minutes for stage 2; -0.20 minutes, 0.20 minutes, and -1.54 minutes for SWS; and 16.21 minutes, 12.55 minutes, and 11.65 minutes for REM, respectively.

In Study 302, the change from baseline in stage 1 to month 1 for daridorexant 25 mg and placebo was 3.64 minutes and 1.81 minutes. For stage 2, the change from baseline to month 1 for daridorexant 25 mg and placebo was 31.54 minutes and 24.09 minutes. For SWS, the change from baseline to month 1 for daridorexant 25 mg and placebo was 0.45 minutes and 0.90 minutes. For REM, the change from baseline to month 1 for daridorexant 25 mg and placebo was 14.19 minutes versus 7.31 minutes. The change from baseline to month 3 in the daridorexant 25 mg and placebo groups were 5.46 minutes and 2.10 minutes for stage 1, 31.36 minutes, and 25.45 minutes for stage 2, -0.91 minutes and 0.65 minutes for SWS, and 13.86 minutes and 6.94 minutes for REM, respectively.

Harms Results

The overall incidence of treatment-emergent AEs (TEAEs) in Study 301 was generally similar across the groups with 41.3%, 39.3%, and 37.2% of patients experiencing TEAEs in the daridorexant 25 mg, daridorexant 50 mg, and placebo groups, respectively. The most common TEAEs across the daridorexant 25 mg, daridorexant 50 mg, and the placebo groups were nasopharyngitis (9.0% versus 7.8% versus 7.8%) and headache (5.5% versus 6.5% versus 3.9%). Serious AEs (SAEs) were reported in 2 patients (0.6%), 3 patients (1.0%), and 7 patients (2.3%) in the daridorexant 25 mg, daridorexant 50 mg, and placebo group, respectively. AEs leading to withdrawals were reported for 7 patients (2.3%), 3 patients (1.0%), and 10 patients (3.2%) in the daridorexant 25 mg, daridorexant 50 mg, and placebo groups, respectively. One patient died due to myocardial infarction, although it was not considered related to treatment.

In Study 302, the overall incidence of TEAEs was similar between the daridorexant 25 mg group (41.2%), and placebo group (36.3%). The most common TEAEs across the daridorexant 25 mg and the placebo groups were nasopharyngitis (4.2% versus 6.5%) and headache (5.2% versus 3.6%). SAEs were reported in 3 patients (1%) and 4 patients (1.3%) in the daridorexant 25 mg and placebo groups, respectively. Four patients (1.3%) in the daridorexant 25 mg group and 7 patients (2.3%) in the placebo group stopped treatment due to AEs. No deaths were reported in Study 302.

Critical Appraisal

Study 301 and Study 302 were multicentre, double-blind, phase III RCTs. Randomization and allocation concealment processes used in the studies were judged to be appropriate. Treatment allocation was stratified based on age (< 65 years or ≥ 65 years), which according to the clinical experts consulted for this review is a clinically important variable, particularly with regards to harms (i.e., morning sedation and night dizziness) and the risk of injury due to fall. Overall, baseline characteristics were generally balanced and similar across the treatment groups in both studies. The treatment discontinuations were relatively infrequent (7.1% to 9% in Study 301 and 5.8% to 7.4% in Study 302), and most of the patients in Study 301 and Study 302 completed the double-blinded treatment period; thus, the risk of attrition bias was considered low. In

both studies, the overall rate of missing data was low (< 10% missing) for all relevant outcomes. Low overall missingness and balanced discontinuation rates across groups reduced concerns related to this potential overestimation but did not completely rule out bias from informative missingness. Sensitivity analyses using multiple imputation under the missing not at random assumptions further supported the robustness of results, as statistical significance was maintained even under conservative imputations. Therefore, any impact of bias due to missing data on study results was likely low. Multiplicity adjustment using alpha-splitting was conducted for primary and secondary outcomes to control for type I error. Other outcomes (e.g., other efficacy outcomes and exploratory outcomes) were not adjusted for multiplicity, so there is an increased risk of false-positive conclusions for statistically significant results. The primary outcomes in both studies were objectively measured using PSG during sleep studies, while subjectively measured outcomes were captured using self-assessment of the patient's sleep or using validated questionnaires. Although PSG provides objective data on sleep parameters and is less prone to reporting bias, its results may not fully capture real-world sleep patterns. Sleep disturbances related to the sleep study setting may alter sleep architecture and limit the accuracy and generalizability of PSG results. According to the clinical experts consulted for this review, patients' self-report of their sleep may not align with the more objective measures. They noted, for example, patients with insomnia have been found to overestimate the time taken to fall asleep (sleep onset latency) and underestimate the total sleeping time. The clinical experts emphasized that insomnia is largely a subjective condition and that sleep complaints are very individualized; therefore, self-reported sleep quality and perceived changes in patients' sleep may be more clinically meaningful than PSG-derived metrics. However, subjective measures may be more prone to bias, including recall bias and placebo effects, that cannot be easily measured or accounted for, making it difficult to determine the true magnitude and certainty of treatment effects. Thresholds of clinical significance for all relevant outcomes, except for sleep quality by VAS were provided by the sponsor. According to the clinical experts consulted for this review, these provided thresholds were clinically relevant and acceptable.

There were several limitations in the included studies that could affect the generalizability of results to clinical settings in Canada. Among the patients who were screened for the trials, most patients in both studies were unsuccessful in screening (72.4% in Study 301 and 74.9% in Study 302). The most common reason for unsuccessful screening was not meeting the inclusion and exclusion criteria, although the submission did not provide any additional details on the exact criteria that were unsuccessful during screening. Patients who did not meet specific sleep parameters on PSG, and those with comorbidities (e.g., acute or unstable psychiatric conditions) were excluded. According to the clinical experts, PSG or other sleep studies are not used to diagnose CID and are not routinely performed in clinical settings for patients with CID. Also, patients who were excluded based on comorbidities could have otherwise been potential candidates for treatments with daridorexant. Thus, the screening process may have led to a study population that do not reflect the broader population with CID in Canada, thereby limiting the generalizability of the results. While the mean age, duration of disease, and the distributions of sex in the study populations were consistent with settings in Canada, the clinical experts noted that the proportion of patients who identified as Asian were considerably lower in the studies (especially Study 301) compared to those settings in Canada. It was unclear whether this could affect the study results beyond cultural differences related to sleep among different racial groups. According to the Health Canada product monograph, daridorexant is contraindicated for patients who

use strong CYP3A4 inhibitors, although daridorexant 25 mg is indicated for patients receiving moderate CYP3A4 inhibitors (or those with moderate hepatic impairment). However, the use of moderate or strong CYP3A4 inhibitors was prohibited during the studies, and those unwilling or unable to discontinue those medications were excluded from both studies. Therefore, any interpretation of efficacy or harms results in the daridorexant 25 mg treatment group was challenging. Several medications, including concomitant pharmacological treatments for insomnia or other central nervous system (CNS)-related medications, were prohibited in the studies. According to the clinical experts, patients with CID observed in clinical settings in Canada would often be taking 1 or more CNS-related medications prohibited in the studies. While only a minority of patients in Canada receive CBT-I as first-line therapy, the clinical experts noted that the proportion would likely be higher than that observed in the trials ($n = 3$ [0.3%] in Study 301, and none in Study 302). As previously noted, sleep studies are not used in clinical settings to diagnose or assess insomnia, instead, patients are usually interviewed about their sleep and how they feel. Additionally, subjective measures used in the studies such as IDSIQ, ISI, or SDQ are not routinely used in clinical practice, per the clinical experts consulted for this review.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- efficacy outcomes (sleep maintenance, sleep onset, sleep duration, and sleep quality)
- harms outcomes (SAEs).

Table 1: Summary of Findings for Daridorexant 50 mg vs. Placebo for Patients With CID

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Daridorexant 50 mg (95% CI)	Placebo (95% CI)	Difference (97.5% CI)		
Sleep maintenance							
LS mean change from baseline in WASO at 3 months, minutes Follow-up:3 months	620 (1 RCT)	NA	−29.41 (−33.40 to −25.43)	−11.11 (−15.13 to −7.09)	−18.30 (−24.76 to −11.85) ^a	Low ^{b,c}	Daridorexant may result in a reduction (improvement) in sleep maintenance (the time spent awake after onset of persistent sleep) at 3 months compared with placebo. The clinical importance of the reduction is unclear.
Sleep onset							
LS mean change from baseline in LPS, minutes Follow-up: 3 months	620 (1 RCT)	NA	−34.80 (−38.118 to −31.490)	−23.13 (−26.464 to −19.803)	−11.67 (−17.027 to −6.320) ^a	Low ^{b,d}	Daridorexant may result in a reduction (improvement) in sleep onset (LPS: time from wakefulness to 10 consecutive minutes of sleep) at 3 months compared with placebo. The clinical importance of the reduction is unclear.
Sleep duration							
LS mean change from baseline in sTST, minutes Follow-up: 3 months	620 (1 RCT)	NA	57.67 (51.17 to 64.17)	37.90 (31.39 to 44.40)	19.77 (9.30 to 30.24) ^a	Low ^{e,f}	Daridorexant may result in an increase in subjective total sleep duration at 3 months compared with placebo. The clinical importance of the increase is unclear.
Sleep quality							
Mean change from baseline in Sleep Diary Questionnaire VAS Follow-up: 3 months	620 (1 RCT)	NA	Daridorexant 50 mg: 20.21 (22.15) Placebo: 13.95 (18.85) Difference: NR			Very low ^{a,h}	The evidence is very uncertain about the effect of daridorexant on change from baseline in sleep diary questionnaire VAS when compared with placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Daridorexant 50 mg (95% CI)	Placebo (95% CI)	Difference (97.5% CI)		
Harms							
Proportion of patients with 1 or more SAEs Follow-up: end of study	620 (1 RCT)	NA	10 per 1,000	23 per 1,000	NR	Moderate ^{i,j}	Daridorexant 50 mg likely results in little to no difference in the occurrence of SAEs when compared with placebo.

CI = confidence interval; LPS = latency to persistent sleep; LS = least squares; NA = not applicable; NR = not reported; RCT = randomized controlled trial; SAE = serious adverse event; sTST = subjective total sleep time; VAS = visual analogue scale; vs. = versus; WASO = wake after sleep onset.

Notes: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

^aAfter hypothesis testing adjusting for multiplicity, the alpha or threshold of significance was estimated to be 0.025. Thus, 97.5% CIs are reported for these between-group differences.

^bRated down once for serious indirectness. The outcomes were measured using polysomnography. According to the clinical experts, polysomnography is not used in clinical settings to assess efficacy of treatment. The external validity of the trial is limited due to the large number of patients excluded at screening.

^cRated down once for serious imprecision. Based on a minimum important difference threshold of 20 minutes, the point estimate of the effect and the 97.5% CI includes the possibility of a trivial effect as well as a nontrivial effect.

^dRated down once for serious imprecision. Based on a minimum important difference threshold of 10 minutes, the point estimate of the effect is larger than the threshold, but the 97.5% CI includes the possibility of a trivial effect as well as a nontrivial effect.

^eRated down once for serious indirectness. The outcome was self-reported. Clinical experts confirmed that patients are likely to underestimate one's own duration of sleep. The external validity of the trial is also limited due to the large number of patients excluded at screening.

^fRated down once for serious imprecision. Based on a minimum important difference threshold of 30 minutes, the point estimate of the effect as well as the 97.5% CI includes the possibility of a trivial effect as well as a nontrivial effect.

^gAnalysis of this outcome was not adjusted for multiplicity; results are considered as supportive evidence.

^hRated down once for serious indirectness. Rated down twice for very serious imprecision. Absolute difference between the groups with CIs were unavailable. Minimum important difference threshold for this outcome is unclear.

ⁱEven though the external validity of the trial is limited due to the large number of patients excluded at screening, this was not rated down for indirectness.

^jRated down once for serious imprecision. Number of events did not meet optimal information size.

Sources: Details included in the table are from the sponsor's Summary of Clinical Evidence, Clinical Study reports for Study 301 and 302, and additional information provided by the sponsor.

LTE Study

Description of Study

Study 303 was a 40-week LTE study (N = 804) assessing the safety and tolerability of daridorexant in adults and older patients with CID. It was a multicentre, double-blind, placebo-controlled trial conducted across 94 sites in 14 countries, including 7 in Canada. Patients who completed Study 301 or Study 302 were eligible, with patients who previously received placebo rerandomized to either continue placebo or receive daridorexant 25 mg. In total, there were 137 patients receiving daridorexant 50 mg (all from Study 301), 270 receiving daridorexant 25 mg (132 from Study 301 and 138 from Study 302), and 255 patients receiving placebo were rerandomized 1:1 to daridorexant 25 mg (N = 127 [66 from Study 301 and 61 from Study 302], termed ex-placebo to daridorexant 25 mg), and placebo (N = 128). A 30-day safety follow-up period assessed AEs and medications. Among the 662 patients in the 4 relevant treatment groups, 459 (69.3%) completed the study. Demographics and most baseline characteristics were balanced across groups, consistent with prior studies.

Efficacy Results

Change From Baseline in sWASO

Throughout the extension study, mean sWASO reductions from baseline were maintained across treatment groups. At week 36, LSM differences between treatment and placebo groups in the change in sWASO from the confirmatory study baseline was –2.01 minutes (95% CI, –14.71 minutes to 10.68 minutes; P = 0.7554) for the daridorexant 50 mg group and –1.51 minutes (95% CI, –12.65 minutes to 9.62 minutes; P = 0.5148) for the daridorexant 25 mg group.

Change From Baseline in sLSO

In the extension study, mean reductions in sLSO from baseline were observed across all treatment groups, with numerically greater improvements in the active treatment groups compared to placebo. At week 36, the LSM treatment difference in sLSO from confirmatory study baseline compared to placebo was –9.19 minutes (95% CI, –18.45 minutes to 0.07 minutes; P = 0.0517) for the daridorexant 25 mg group and –8.76 minutes (95% CI, –19.34 minutes to 1.82 minutes; P = 0.1044) for the daridorexant 50 mg group.

Change From Baseline in sTST

In the extension study, changes in sTST from confirmatory study baseline were numerically greater for the daridorexant groups than placebo, with the most pronounced change in the daridorexant 50 mg group. The LSM treatment differences in sTST versus placebo at week 36 was 17.77 minutes (95% CI, –0.35 minutes to 35.90 minutes; P = 0.0546) for the daridorexant 50 mg group and 5.26 minutes (95% CI, –10.59 minutes to 21.11 minutes; P = 0.5148) for the daridorexant 25 mg group.

ISI Score

At week 40, the mean change in ISI score was –9.8 for the daridorexant 50 mg group, –8.5 for the daridorexant 25 mg group, –4.3 for the ex-placebo to daridorexant 25 mg group, and –7.5 for the placebo group. A 6-point or greater decrease in ISI score was achieved by 74.7% of patients in the daridorexant

50 mg group, 66.1% in the daridorexant 25 mg group, 35.8% in the ex-placebo group, and 53.9% in the placebo group.

Change From Baseline in SDQ VAS Scores

Improvements from baseline in quality of sleep (VAS) were maintained in all treatment groups throughout the extension study. The mean changes from baseline at week 36 were 27.4 (SD = 23.6), 22.4 (SD = 21.6), 9.7 (SD = 16.3), and 21.9 (SD = 19.2) for the daridorexant 50 mg, daridorexant 25 mg, ex-placebo to daridorexant 25 mg, and placebo groups, respectively. Similar results were reported for all other VAS domain end points.

Change From Baseline in IDISQ Total Score

Mean reductions in IDSIQ total score from baseline were maintained throughout the extension study among patients in the daridorexant 50 mg and 25 mg groups. The LSM treatment differences in IDSIQ total scores versus placebo at week 36 were -9.12 (95% CI, -15.59 to -2.66; $P = 0.0058$) and -4.52 (95% CI, -10.15 to 1.12, $P = 0.11161$), for each of the daridorexant 50 mg group and the daridorexant 25 mg group, respectively.

Harms Results

In Study 303, during the double-blind treatment period up to 30 days after double-blind study treatment end date, the proportion of patients experiencing TEAEs was 40.1%, 38.4%, 38.1%, and 35.2% in the daridorexant 50 mg group, daridorexant 25 mg group, ex-placebo to daridorexant 25 mg group, and placebo group, respectively. Most TEAEs were mild or moderate, with nasopharyngitis being the most common (4.7% to 8.7%). The incidence of SAEs was less than 5.2% in all treatment groups. Most SAEs were reported by a single patient and were not considered related to the study medication, except for 1 case of orthostatic intolerance (daridorexant 25 mg) and 1 of depression or suicidal ideation (placebo). One death occurred in the daridorexant 25 mg group, unrelated to treatment.

In terms of AEs of special interest, less than 3% of patients in each group experienced falls and other events including, hallucinations or sleep paralysis, narcolepsy-like symptoms, and suicide or self-harm were reported by 1 patient each. No patients reported suicidal ideation or behaviour during the double-blind portion of the study or during the placebo run-out period. Benzodiazepine Withdrawal Symptom Questionnaire mean scores were low and similar across treatment groups, with minor changes from the last double-blind assessment to the placebo run-out period. There was no indication of rebound insomnia in any treatment group as assessed by the mean sTST during the placebo run-out period. Next-morning residual effects improved from baseline throughout the study for all treatment groups as assessed by the mean VAS morning sleepiness score.

Critical Appraisal

In the extension study, baseline characteristics were balanced across groups, consistent with the confirmatory studies. However, only patients who completed Study 301 or Study 302 were included, which could bias the results in favour of treatment. Furthermore, patients in the placebo group of Study 303 were already receiving placebo in their respective confirmatory study. Their continued participation suggests they likely responded well to placebo, which may explain their improved sleep-related outcomes (i.e., sTST,

sWASO, and sLSO) reported in the extension study. The study lacked multiplicity adjustments, had many tests, and had no statistical sample size considerations, raising the risk of type I error. High dropout rates (28.5% to 35.2%) could overrepresent patients more likely to benefit from treatment.

Among the 664 patients in the 4 treatment groups assessed, 7 (1.1%) identified as Asian, 38 (5.7%) identified as Black or African American, 2 (0.3%) identified as other, and 421 (63.6%) identified as white, which does not reflect the ethnic diversity seen in patients with CID as expressed by the clinical experts consulted. Additionally, not including individuals with acute and complex mental health conditions and the low percentage of patients (7.3%) with psychiatric disorders in the extension study limits generalizability to this patient population. Clinical experts also noted that tools like ISI and IDSIQ are not commonly used in clinical practice, further limiting generalizability to clinical practice.

Indirect Comparisons

The sponsor determined that it was infeasible and inappropriate to conduct an indirect treatment comparison for daridorexant; thus, no indirect evidence was submitted for this review.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps were submitted by the sponsor for this review.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evidence

Component	Description
Type of economic evaluation	Cost-utility analysis Decision tree
Target population	Adults diagnosed according to the most recent version of the <i>DSM</i> referring to CID.
Treatment	Daridorexant
Dose regimen	50 mg once per night
Submitted price	\$2.36 per 25 mg and 50 mg tablets
Submitted treatment cost	\$861.99 per year
Comparator	No pharmacological treatment
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	1 year
Key data sources	One phase III, double-blind, placebo-controlled trial (Study 301), and a 40-week double-blind, placebo-control, long-term extension study (Study 303)

Component	Description
Submitted results	ICER = \$28,152 per QALY gained versus no pharmacological treatment (incremental costs: \$692; incremental QALYs: 0.025)
Key limitations	• The sponsor's submitted base care compared daridorexant to no pharmacological treatment (referring to the placebo group of Study 301), which is not a relevant comparator for decision-making. Patient input, clinician input, and clinician expert feedback obtained by CDA-AMC indicated that multiple different off-label treatment options such as over-the-counter medication and supplements, benzodiazepines, Z-drugs, antidepressants, and antipsychotics are available and used to treat patients. Patients using these treatments were excluded from Study 301 and the subsequent long-term extension Study 303. • Study 301 and Study 303 did not include patients based on sleep parameters, pharmacological treatments, and comorbid conditions. According to clinician expert feedback obtained by CDA-AMC, this resulted in patients that would be candidates for daridorexant treatment to be excluded from the trial. As such, the clinical effectiveness and cost-effectiveness of daridorexant may not be representative of its use in the full patient population for whom it is likely to be used in clinical practice. • A mapping algorithm was used to derive utility values from ISI scores reported in the clinical trials. While the sponsor's submitted base-case estimates a utility benefit from daridorexant treatment versus no pharmacological treatment, the clinical trials did not demonstrate a clinically meaningful difference in ISI scores between the daridorexant and placebo groups. • There is uncertainty to whether daridorexant would result in a clinically meaningful difference in sleep quality (i.e., Sleep Diary Questionnaire) and daytime functioning (i.e., Insomnia Daytime Symptoms and Impacts Questionnaire) when compared to placebo based on the available clinical evidence. As reported in the CDA-AMC Clinical Review report, both outcomes did not achieve meaningful between-group differences in Study 301. Therefore, it is uncertain if daridorexant provides a clinical benefit for patient important outcomes (i.e., sleep quality and daytime functioning).
CDA-AMC reanalysis results	• There is no comparative clinical evidence against currently available treatments for chronic insomnia, and the sponsor did not submit indirect evidence due to feasibility. As noted in the CDA-AMC Clinical Review report, outcomes evaluated in the submitted clinical studies were clinically relevant, but it remains uncertain whether daridorexant resulted in clinically meaningful improvements compared to placebo.

CDA-AMC = Canada's Drug Agency; CID = chronic insomnia disorder; *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*; ICER = incremental cost-effectiveness ratio; ISI = Insomnia Severity Index; QALY = quality-adjusted life-year.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: uncertainty in the size of the target population as the sponsor requested a narrower reimbursement population during the course of the review period; omission of relevant off-label comparators; uncertainty associated with the market uptake of daridorexant; duration of treatment does not reflect clinical disease management of patients with chronic insomnia; and uncertainty associated with estimating eligible patients based on drug plan enrolment. The 3-year budget impact of funding daridorexant for the management of adult patients with CID according to the *DSM* was estimated to be \$127,504,358 (year 1: \$26,986,827; year 2: \$45,438,847; year 3: \$55,078,684). The budget impact of funding daridorexant for the reimbursement requested population is unknown but is expected to be smaller than the CDA-AMC reanalysis.

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for daridorexant for insomnia. In their request, the sponsor identified the following issues:

- The sponsor notes that CDEC's insistence on inappropriate comparators that are not suitable for chronic insomnia undermines the CID-specific evaluation framework, creating inconsistency, and imposes an unrealistic evidentiary standard. The sponsor urged CDEC to further clarify and explain why the negative recommendation cites the broader Health Canada indication for daridorexant, when the sponsor intended the review to be limited to CID, where the rest of the recommendation refers to the CID-focused evidence, as per the requested reimbursement criteria.
- The sponsor urges CDEC to revise its recommendation to reflect the fundamentally subjective nature of CID, emphasizing that validated patient-reported outcomes are the most relevant for assessing real-world benefit, as supported by clinicians, patients, and regulators. The sponsor stated that the draft recommendation should be revised to align with consulted parties and clearly acknowledge and recognize the fundamentally subjective nature of CID as well as the validated subjective measures of sleep and daytime function as the most clinically relevant outcomes to determine meaningful benefit.
- The sponsor highlighted that the evaluation of meaningful benefit of daridorexant was based on expert-derived MIDs for objective measures, rather than validated patient-reported outcome MIDs, which they note lacks methodological rigour, undervalues concordant trial results, and does not adhere to established methodology advocated by regulatory guidelines thereby misrepresenting daridorexant and its ability to address what matters most to patients. The sponsor requests that CDEC rely on MIDs specifically validated in a CID population.
- The sponsor requests that CDEC remove the concept of using MIDs as null hypothesis thresholds for statistical inference as this undermines the meaningfulness of outcomes that are important to patients.
- The sponsor requests that CDEC acknowledge that no comparative decision-grade data exists, as previously acknowledged by CDA-AMC in their previous reviews of insomnia, particularly for continuous treatment of at least 3 months and up to 12 months. Therefore, the sponsor emphasized that the statement from CDEC that several network meta-analyses were published in the CID therapeutic context is incorrect and must be revised.
- The sponsor states that because the safety profile of daridorexant is strongly congruent with patient preferences in CID, it should, by itself, warrant a positive recommendation. Further, the sponsor notes that CDEC (and CDA-AMC) acknowledges the superior safety of daridorexant, while simultaneously demanding comparative efficacy data where no viable comparator data exists. As such, the sponsor requests that CDEC give greater weight to the superior safety of daridorexant and the alignment with key unmet needs. The sponsor also requested that CDEC reconsider the overall weight placed on comparative efficacy evidence given the alignment of daridorexant with the therapeutic gaps identified by patients and clinicians, including restorative sleep, reduced next-day impairment, and low risk of dependence, which were all recognized by CDA-AMC.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- feedback from 2 clinical specialists with expertise in diagnosing and treating patients with insomnia
- feedback on the draft recommendation from 2 patient groups
- feedback on the draft recommendation from 9 clinician groups
- feedback on the draft recommendation from the public drug plans that participate in the reimbursement review process
- feedback on the draft recommendation from the sponsor.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunskey, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: May 28, 2025

Regrets: Three expert committee members did not attend.

Conflicts of interest: None.

Members of the Committee (Reconsideration Meeting)

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunskey, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Reconsideration meeting date: September 24, 2025

Regrets: Four expert committee members did not attend.

Conflicts of interest: None.



Canada's Drug Agency
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