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CADTH Reimbursement Recommendation

Lemborexant (Dayvigo)

Indication: Lemborexant is indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Sponsor: Eisai Limited

Final recommendation: Do not reimburse

CADTH

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Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the CADTH Drug Reimbursement Review Confidentiality Guidelines.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Dayvigo?

CADTH recommends that Dayvigo not be reimbursed by public drug plans for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Why Did CADTH Make This Recommendation?

- Two clinical trials showed that, compared to placebo, Dayvigo resulted in improvements in the time it takes to fall asleep, the time spent awake after initially falling asleep, and the time spent sleeping divided by the total time spent in bed measured during sleep studies.
- It was uncertain whether the effect of Dayvigo was enough to make a clinically meaningful improvement for the sleep outcomes measured using patients' sleep diaries.
- Based on the evidence reviewed, it is uncertain whether Dayvigo offers a meaningful clinical benefit over other treatments used for insomnia. There was not enough evidence to conclude that Dayvigo meets patients' needs for a treatment with long-term effectiveness that results in uninterrupted and restorative sleep, less stress and anxiety, improved productivity, improved relationships, and fewer side effects compared to other treatments for insomnia. It was also unclear if patients receiving Dayvigo would be able to manage their sleep problems without becoming dependent on the medication.

Additional Information

What Is Insomnia?

Insomnia is a sleep disorder characterized by difficulty falling sleep, 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. Insomnia can be diagnosed as a disorder on its own or as a symptom associated with other medical conditions. It is estimated that between 12% and 24% of people in Canada are affected by insomnia.

Unmet Needs in Insomnia

There is a need for insomnia treatments with long-term effectiveness that result in uninterrupted and restorative sleep, less stress and anxiety, and improved productivity and 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 Dayvigo Cost?

Treatment with Dayvigo is expected to cost approximately $555 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that lemborexant (LEM) not be reimbursed for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Rationale for the Recommendation

Although 2 randomized, controlled, double-blind, phase III trials (SUNRISE 1, N = 1,006 and SUNRISE 2, N = 971) in adults with insomnia showed that treatment with LEM resulted in statistically significant improvements in measures of sleep onset, sleep maintenance, and sleep efficiency compared with placebo, it was uncertain whether the magnitude of the treatment effect was clinically meaningful for multiple outcomes due to variability in results, missing data, lack of control for multiplicity, lack of an estimated minimum important difference (MID), or the MID was not met. The SUNRISE 1 trial showed that LEM resulted in clinical benefit for adult patients with insomnia compared to placebo in objective measures of sleep onset, sleep maintenance, and sleep efficiency after 30 days of treatment compared to placebo. However, there was variability in the results (i.e., mean changes from baseline with large standard deviations [SDs] and least squares mean [LSM] treatment differences with wide confidence intervals [CIs]). The SUNRISE 1 trial suggested a benefit with LEM in wake after sleep onset in the second half of the night (WASO2H) compared to zolpidem (ZOL) extended-release, but it was uncertain if this result was clinically meaningful because this outcome did not have an established MID or clinically important threshold. In SUNRISE 2, all primary and key secondary outcomes were for subjective sleep diary measures after 6 months of treatment, and few reached the suggested thresholds for a clinically important effect. ZOL extended-release was an active comparator in SUNRISE 1, but there is no direct evidence comparing the efficacy and safety of LEM relative to other drugs commonly used to treat insomnia in clinical practice in Canada. The indirect evidence comparing LEM to other treatments is uncertain due to numerous limitations, precluding definitive conclusions. Based on the direct and indirect evidence available, CDEC could not conclude how the efficacy or safety profile of LEM would compare to other drugs.

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

Discussion Points

- The sponsor requested a reconsideration of the initial draft recommendation to not reimburse LEM for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. CDEC discussed each of the issues identified by the sponsor in its request for reconsideration.

- CDEC noted that it was unclear whether LEM would address the needs identified as important to patients, including uninterrupted and restorative sleep, more effective treatment options, fewer side effects, and long-term treatment effectiveness. No conclusions could be drawn regarding whether treatment with LEM confers a benefit for patient-reported outcomes (e.g., Insomnia Severity Index [ISI] items 4 to 7, Fatigue Severity Scale [FSS], the 3-Level EQ-5D [EQ-5D-3L], and Patient Global Impression [PGI]-Insomnia) due to the lack of adjustment for multiple comparisons and no established MID in patients with insomnia. In their feedback on the initial draft recommendation, clinician groups indicated that MIDs and clinically important thresholds have not been well established in this disease area because many drugs in Canada are used off-label and have little or no supportive evidence of efficacy or safety. In the reconsideration meeting, the clinical expert highlighted that insomnia is a subjective disorder, which means the patient's perception of LEM's efficacy and their experience of insomnia may not be captured by clinical trial data. CDEC acknowledged that this is a limitation of the evidence but could not conclude whether the results for these outcomes would be clinically meaningful. In addition, due to limitations of the indirect evidence, it was uncertain whether LEM is more effective or has fewer side effects than other drugs used to treat insomnia in Canada.
- CDEC discussed that it is uncertain how LEM compares to the drugs commonly used in Canada to treat insomnia because the indirect evidence was uncertain due to limitations of the sponsor-submitted and published network meta-analyses (NMAs) (e.g., risk of bias in the individual studies, heterogeneity in the pairwise comparisons, suspected publication bias, imprecise effect estimates) and differences in conclusions for some outcome comparisons across NMAs. CDEC discussed the new indirect evidence provided by the sponsor in their request for reconsideration but determined it was not sufficient to allow for a conclusion on the clinical benefit of LEM over the currently available treatment options because the NMA was associated with similar methodological limitations as the 2 NMAs previously reviewed by CDEC and the results were imprecise.
- Patients also indicated they want treatments for insomnia to result in less stress and anxiety, and improved productivity and relationships with family members and colleagues. CDEC noted that it is unknown whether LEM has a beneficial effect on stress, anxiety, productivity, or relationships as this was not assessed in the SUNRISE 1 and SUNRISE 2 trials.
- CDEC discussed the relevance of ZOL to Canadian clinical practice and the comparability of ZOL versus zopiclone. CDEC noted that ZOL, which was the active comparator in the SUNRISE 1 trial, is not commonly used in Canada and the extended-release formulation used in the trial is not available in Canada. In their feedback on the initial draft recommendation, clinician groups indicated that ZOL extended-release and zopiclone are comparable as they are of the same drug class and have a shared mechanism; therefore, the clinicians were of the view that a lack of direct comparison was not a critical issue. However, CDEC concluded that their pharmacokinetic profiles are not identical and it is unclear how ZOL compares to zopiclone due to limited evidence comparing the 2 Z-drugs.
- CDEC discussed that somnolence and the risk of falls are key concerns associated with pharmacological treatment of insomnia. In both trials, rates of somnolence were higher among patients who received LEM than the comparators. CDEC noted that falls were rare in the SUNRISE 1 and SUNRISE 2 trials. Postural stability was assessed but the results were uncertain. CDEC noted that the safety profile of LEM in the clinical trials may not reflect what is observed in clinical practice with long-term use. Even though

indirect evidence suggested that LEM is associated with a reduction in the odds of falls when compared to other drugs, the results were too imprecise, with wide CIs, to draw conclusions. CDEC noted that dependency is also a concern with drugs used to treat insomnia. The committee also noted that the SUNRISE 1 and SUNRISE 2 studies assessed rebound insomnia with a 2-week follow-up period, during which between 9% and 25% of the patients who received either LEM 5 mg (LEM5) or LEM 10 mg (LEM10) experienced rebound insomnia. CDEC noted that the rates of rebound insomnia and withdrawal symptoms or dependence were lower for LEM compared to ZOL in the SUNRISE 1 trial; however, there were missing data and the differences between groups were not statistically tested.

- During the reconsideration meeting, CDEC discussed the efficacy data regarding LEM and noted that the SUNRISE 1 and SUNRISE 2 trials included an enriched study population. The trials only included patients who adhered to study protocols, sleep diaries, and alcohol and caffeine restrictions, and CDEC noted there was a high proportion of screening failures during the prerandomization phase. In addition, CDEC noted that insomnia may precede, accompany, or follow other conditions. The SUNRISE 1 and SUNRISE 2 trials excluded patients with an Apnea-Hypopnea Index (AHI) score of at least 10 (adults aged 18 to 64 years in the SUNRISE 2 trial) or greater than 15 (all patients in the SUNRISE 1 trial and patients older than 64 years in the SUNRISE 2 trial), Beck Anxiety Inventory score greater than 15, or Beck Depression Inventory–II score greater than 19. CDEC noted that patients with moderate to severe sleep apnea, anxiety, and depression would not have been enrolled in the SUNRISE trials. Furthermore, patients with a history of drug or alcohol dependency or use disorder were also excluded from the trials. With an enriched study population, the treatment effects observed could be larger than what would be observed in clinical practice. In addition, the generalizability of the results from the studies to the patient groups excluded from the studies is uncertain.
- During the reconsideration meeting, CDEC discussed the feedback from patient groups and clinician groups emphasizing the need for treatment options that are more effective and safer compared to existing treatments for insomnia or nonpharmacological treatment. The clinician groups and clinical expert highlighted that other medications used to treat insomnia are associated with considerable harms, and they are of the view that the safety profile of LEM is favourable. CDEC acknowledged there is a lack of safe pharmacological treatments for insomnia; however, the committee was uncertain whether LEM would be safer than alternative treatments outside trial conditions. CDEC noted that the duration of treatment with LEM was 30 days in the SUNRISE 1 trial and up to 12 months in the SUNRISE 2 trial; therefore, data on long-term effectiveness and safety are limited to this time frame. Furthermore, CDEC noted that safety demonstrated in the clinical trials may not always be generalizable to real-world practice. There were limitations to the data provided in the Periodic Safety Update Report (PSUR) included in the sponsor's request for reconsideration (e.g., data were presented in aggregate, including people who do not have insomnia). CDEC discussed that there is still uncertainty in the available evidence that limits its ability to draw a firm conclusion that LEM is a safer option than other drugs.

Background

Insomnia disorder is the most common sleep disorder and, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), is described as being

dissatisfied with the quality or quantity of sleep, difficulty initiating and/or maintaining sleep, and is associated with daytime impairment. The DSM-5 criteria include sleep disturbances occurring at least 3 nights per week for at least 3 months. In Canada, the prevalence is estimated to be between 12% and 24% and the incidence is estimated to be between 3.8% and 7.3% per year. Insomnia can be diagnosed as a disorder on its own or as a symptom associated with many other medical conditions and has been closely linked to reduced life expectancy and increased economic costs through lost productivity, workplace and motor vehicle accidents (MVAs), and greater health care utilization. Per the Alberta Medical Association's Clinical Practice Guidelines, insomnia can be treated and managed in a primary care setting or by a specialist. Nonpharmacological treatment options such as sleep hygiene education and cognitive behavioural therapy for insomnia (CBT-I) are recommended as an initial treatment. Pharmacological treatments include benzodiazepine receptor agonists, dual orexin receptor antagonists, histamine receptor antagonists, and melatonin receptor agonists. Off-label medications that have sedating effects are generally not recommended as a first-line treatment due to the lack of efficacy and safety evidence in this population. Long-term use of hypnotics is discouraged as the studies supporting their approval were based on short-term use; hypnotics are not recommended as a first-line treatment option.

LEM is a dual orexin receptor antagonist indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. The recommended dose is 5 mg once per night and may be increased to the maximum recommended dose of 10 mg based on clinical response and tolerability. LEM is taken orally once per night within a few minutes before going to bed with at least 7 hours before planned awakening time.

Sources of Information Used by the Committee

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

- a review of 2 randomized controlled trials (RCTs) in adults with insomnia
- patients' perspectives gathered by 3 patient groups, the Mood Disorder Society of Canada (MDSC), Migraine Canada, and Menopause Chicks
- input from the public drug plans that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with insomnia
- input from 2 clinician groups, including the Canadian Consortium of Sleep and Sleep Interested Physicians (CCSSP) and the National Advisory Board
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the request for reconsideration (described in the following).

Stakeholder Perspectives

Patient Input

CADTH received input from 3 patient groups: the MDSC, Migraine Canada, and Menopause Chicks. The 3 groups conducted surveys and interviews with patients and caregivers to inform their input. Respondents from all 3 patient groups indicated that sleep problems significantly impacted their quality of life, energy level, cognitive function, mood the next day, and daytime activities. Most respondents reported having tried various treatments (e.g., benzodiazepines, Z-drugs) for sleep problems. Many reported being dissatisfied and that they discontinued treatment due to side effects such as next day sedation and cognitive impairment, and fear of developing a substance use disorder. The groups indicated the following as key outcomes for patients and caregivers: uninterrupted and restorative sleep, greater access to treatment, more effective treatment options, long-term effectiveness, fewer side effects, less stress and anxiety, and improved productivity and relationships. The MDSC input included 3 respondents who had experience with LEM and accessed the drug through private health insurance. They described being able to manage their sleep problems without becoming dependent on the medication or experiencing serious side effects, and without feeling lethargic and sleepy the next morning.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

The clinical expert consulted for this review stated that the current goals of treatment are to improve sleep initiation, maintenance, and terminal insomnia leading to restorative sleep. According to the clinical expert, CBT-I is the first-line treatment for insomnia, but many patients have limited access to and/or success with this option, thus pharmacotherapy is often used in addition to or in place of CBT-I. Per the expert, when a medication is used for extended periods of time, a patient may have a waning response or no response. At this point it can be difficult to withdraw the therapy if the patient has developed tolerance to the drug and the patient may experience rebound insomnia. Another concern raised by the clinical expert was the risk of cognitive and behavioural changes the next morning that can lead to falls and other dangers, particularly for patients who are older.

The clinical expert suggested that LEM may be a first-line pharmacological treatment for insomnia and noted that it would be necessary to determine how to optimally transition from other currently available medications (e.g., Z-drugs) to LEM. The expert indicated that most patients with insomnia may be candidates for treatment with LEM, except for those who are pregnant, nursing, or have narcolepsy. According to the clinical expert, patients are asked general questions about their sleep rather than taking measurements in clinics, which does not tend to vary among physicians, according to the expert, who also indicated that few clinics are performing sleep studies for insomnia (except where another sleep disorder is suspected) because access is limited across Canada.

The expert noted that chronic insomnia generally does not go away and tends to worsen with age, menopause, or as a result of other major negative life events. The expert suggested that a patient may wish to trial being off medication and can be supported by additional sleep management tools such as CBT-I. When deprescribing a medication, the clinical expert would observe for a return of symptoms or rebound insomnia. Per the clinical expert, family physicians or psychiatrists typically treat insomnia.

Clinician Group Input

CADTH received input from 2 clinician groups: the CCSSP and the National Advisory Board. The clinician group input was aligned with that given by the clinical expert consulted by CADTH.

Drug Program Input

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

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two double-blind, phase III, RCTs, SUNRISE 1 and SUNRISE 2, were included in the systematic review of LEM.

The SUNRISE 1 trial (N = 1,006) was designed to assess the safety and efficacy of LEM5 and LEM10 for 30 days in females who were 55 years or older and males who were 65 years or older, all of whom had insomnia disorder according to the DSM-5. Comparators included ZOL extended-release 6.25 mg and appearance-matched placebos (PBOs) for both active compounds. The primary outcome was latency to persistent sleep (LPS) and key secondary outcomes were wake after sleep onset (WASO), WASO2H, and sleep efficiency as measured by polysomnography (PSG). Other secondary and exploratory outcomes important to the CADTH review included patient-reported outcomes such as the EQ-5D-3L, ISI, FSS, PGI-Insomnia, and quality of sleep questionnaires. Patients had a mean age of 63.9 years (SD = 6.81 years) and 86.4% were female. At baseline, mean LPS was approximately 45 minutes, mean WASO was around 114 minutes, mean WASO2H was 77 minutes, and mean sleep efficiency was 68%.

The SUNRISE 2 trial (N = 971) was designed to assess the long-term safety and efficacy of LEM5 and LEM10 for up to 12 months in adults 18 years or older who had insomnia disorder according to the DSM-5. The first 6 months of SUNRISE 2 consisted of 3 treatment groups: LEM5, LEM10, and PBO. For the next 6 months of the trial, patients who were randomized to PBO were rerandomized to active treatment (i.e., LEM5 or LEM10) for the remainder of the trial. The primary outcome was subjective sleep onset latency (sSOL) and key secondary

outcomes were subjective WASO (sWASO) and subjective sleep efficiency as recorded in the sleep diary. Other secondary and exploratory outcomes important to the CADTH review were the same as the patient-reported outcomes listed for the SUNRISE 1 trial. Patients had a mean age of 54.5 years (SD = 13.80 years) and 68.2% were female. At baseline, mean sSOL was approximately 64 minutes, sWASO was 134 minutes, and subjective sleep efficiency was 62%.

Efficacy Results

Statistical testing was conducted based on a gate-keeping procedure for both studies. In the SUNRISE 1 trial, the following outcomes were controlled for multiplicity: LPS, sleep efficiency, WASO, and WASO2H. In the SUNRISE 2 trial, the following outcomes were controlled for multiplicity: sSOL, subjective sleep efficiency, and sWASO.

HRQoL and Severity of Symptoms

The clinical expert emphasized the importance of patient-reported outcomes such as the EQ-5D-3L, ISI, FSS, PGI-Insomnia, and quality of sleep questionnaires. For the EQ-5D-3L visual analogue scale in the SUNRISE 1 trial, the LSM treatment difference for LEM10 versus PBO was 2.53 (95% CI, 0.69 to 4.38) and for LEM5 versus PBO was 0.52 (95% CI, −1.32 to 2.37). In the SUNRISE 2 trial, the LSM treatment difference for LEM10 versus PBO was 1.04 (95% CI, −1.36 to 3.43) and for LEM5 versus PBO was −0.96 (95% CI, −3.31 to 1.39). All patient-reported outcome questionnaires were other secondary or exploratory outcomes and were not adjusted for multiplicity; therefore, definitive conclusions could not be made from the results.

Sleep Latency (Sleep Onset): LPS and sSOL

In the SUNRISE 1 trial, the least squares geometric mean treatment ratio for LPS for LEM10 versus PBO was 0.72 (95% CI, 0.63 to 0.83; P < 0.0001) and for LEM5 versus PBO was 0.77 (95% CI, 0.67 to 0.89; P = 0.0003).

In the SUNRISE 2 trial, the least squares geometric mean treatment ratio for LPS for LEM10 versus PBO was 0.70 (95% CI, 0.61 to 0.81; P < 0.0001) and for LEM5 versus PBO was 0.73 (95% CI, 0.64 to 0.84; P < 0.0001).

Waking After Sleep Onset (Sleep Maintenance): WASO, WASO2H, and sWASO

In the SUNRISE 1 trial, the LSM treatment differences for WASO for LEM10 versus PBO was −25.35 minutes (95% CI, −31.36 to −19.34 minutes; P < 0.0001) and for LEM5 versus PBO was −23.96 minutes (95% CI, −29.98 to −17.95 minutes; P < 0.0001). The LSM treatment differences for WASO2H for LEM10 versus ZOL was −8.00 minutes (95% CI, −12.53 to −3.47 minutes; P = 0.0005) and for WASO2H for LEM5 versus ZOL was −6.65 minutes (95% CI, −11.15 to −2.15 minutes; P = 0.0038).

In the SUNRISE 2 trial, the LSM treatment differences for LEM10 versus PBO was −12.67 minutes (95% CI, −22.38 to −2.96 minutes; P = 0.0105) and for LEM5 versus PBO was −17.47 minutes (95% CI, −27.31 to −7.64 minutes; P = 0.0005).

Sleep Efficiency: Sleep Efficiency and Subjective Sleep Efficiency

In the SUNRISE 1 trial, the LSM treatment differences for LEM10 versus PBO was 8.03% (95% CI, 6.57 to 9.49%; P < 0.0001) and for LEM5 versus PBO was 7.07% (95% CI, 5.61 to 8.54%; P < 0.0001).

In the SUNRISE 2 trial, the LSM treatment differences for LEM10 versus PBO was 4.67% (95% CI, 2.37 to 6.96%; P < 0.0001) and for LEM5 versus PBO was 4.55% (95% CI, 2.24 to 6.86%; P = 0.0001).

Harms Results

Adverse Events

In the SUNRISE 1 study, approximately one-third of patients experienced a treatment-emergent adverse event (TEAE), and rates were relatively similar among all groups: 82 (30.6%), 74 (27.8%), 93 (35.4%), and 53 (25.4%) patients in the LEM10, LEM5, ZOL, and PBO groups, respectively. In the SUNRISE 2 study, more than half of the patients experienced a TEAE and rates were similar among all groups: 187 (59.6%), 192 (61.1%), and 200 (62.7%) of patients in the LEM10, LEM5, and PBO groups, respectively. The most common events in both studies were headache, somnolence, and nasopharyngitis.

Serious Adverse Events

Serious adverse events (SAEs) were rare in both studies. In the SUNRISE 1 trial, 2 (0.8%) and 4 (1.5%) patients in the LEM5 and ZOL groups, respectively, experienced at least 1 SAE. No patients in the LEM10 or PBO groups reported an SAE. In the SUNRISE 2 trial, 9 (2.9%), 7 (2.2%), and 5 (1.6%) patients in the LEM10, LEM5, and PBO groups, respectively, experienced at least 1 SAE. No SAE occurred in more than 1 patient per treatment group.

Withdrawals Due to Adverse Events

In general, there were few withdrawals from treatment due to adverse events (AEs) in both studies. In the SUNRISE 1 study, 3 (1.1%), 2 (0.8%), 7 (2.7%), and 2 (1.0%) patients in the LEM10, LEM5, ZOL, and PBO groups, respectively, stopped treatment due to an AE. No events occurred in more than 1 patient in any treatment group. In the SUNRISE 2 trial, 26 (8.3%), 13 (4.1%), and 12 (3.8%) patients in the LEM10, LEM5, and PBO groups, respectively, stopped treatment due to an AE. The following events occurred in more than 1 patient in any group: headache, somnolence, nightmare, and palpitations.

Mortality

No deaths were reported in the SUNRISE 1 or SUNRISE 2 trials.

Notable Harms

In both studies, rates of somnolence were numerically higher among patients who received LEM10 compared to those who received LEM5 (7.1% versus 4.1% in the SUNRISE 1 study and 13.1% versus 8.6% in the SUNRISE 2 study) and were greater than either ZOL (1.5%) or PBO (1.9%) in the SUNRISE 1 trial or PBO (1.6%) in the SUNRISE 2 trial.

Falls were rare in the SUNRISE 1 (1.5% in the LEM5 group and 0% for all other groups) and SUNRISE 2 (1.6% in each of the LEM10 and LEM5 groups and 3.1% for PBO) trials.

A road traffic accident (MVA for the CADTH systematic review protocol) was described for 1 patient who received ZOL in the SUNRISE 1 trial and no other treatment groups reported an MVA. In the SUNRISE 2 trial, 1 patient each in the LEM10 and PBO groups reported an MVA and no MVAs were reported in the LEM5 group.

Reports of hallucinations were rare in both studies. In the SUNRISE 1 trial, tactile hallucination was reported for 1 patient who received LEM10 (0 patients for all other treatments). In the SUNRISE 2 trial, hypnagogic hallucination was reported for 3 patients (2 patients who

received LEM10 and 1 patient who received LEM5) while hypnopompic hallucination was reported for 1 patient who received LEM10. The PBO group did not have any reports of hallucinations.

No intentional overdoses were reported in the SUNRISE 1 trial. Intentional overdoses were reported for 2 patients who received LEM5, 1 patient who received PBO, and 0 patients who received LEM10 in the SUNRISE 2 trial.

Impaired driving and workplace accidents were not reported in either trial.

Postural instability was assessed in the SUNRISE 1 trial. On days 2 to 3, the LSM treatment difference between LEM10 and PBO was 2.91 units (95% CI, −0.28 to 6.10 units) and between LEM5 and PBO was 2.49 units (95% CI, −0.70 units to 5.67 units). The LSM treatment difference between LEM10 and ZOL was −4.29 units (95% CI, −7.32 units to −1.26 units) and between LEM5 and ZOL was −4.71 units (95% CI, −7.73 units to −1.70 units). On days 30 to 31, the LSM treatment difference between LEM10 and PBO was −0.58 units (95% CI, −3.68 units to 2.53 units) and between LEM5 and PBO was −0.71 units (95% CI, −3.80 units to 2.38 units). The LSM treatment difference between LEM10 and ZOL was −2.57 units (95% CI, −5.53 units to 0.39 units) and between LEM5 and ZOL was −2.70 units (95% CI, −5.64 units to 0.23 units). As there was no adjustment for multiplicity, the results are uncertain.

Impaired attention was assessed in the SUNRISE 1 study using 2 components of the Cognitive Performance Assessment Battery: power of attention and continuity of attention. On both days 2 to 3 and days 30 to 31, the mean change from baseline for power of attention decreased for the PBO group and increased for the LEM10, LEM5, and ZOL groups. On days 2 to 3, the mean change from baseline for continuity of attention increased for the LEM5 group and decreased for the LEM10, PBO, and ZOL groups. On days 30 to 31, the mean change from baseline for continuity of attention decreased for all groups. Since there was no adjustment for multiplicity for this outcome, conclusions based on the results cannot be drawn with certainty.

In the SUNRISE 1 trial, differences in reports of rebound insomnia during the follow-up period between the treatment groups were not tested statistically. The frequency of rebound insomnia appeared similar between the LEM10 and LEM5 groups based on sSOL measures (17% to 21% for the first 7 nights of follow-up and 22% to 24% for the last 7 nights of follow-up) and proportions were numerically higher for the ZOL and PBO groups (23% to 27% for the first 7 nights and 23% to 27% for the last 7 nights). The results using sWASO measures were similar for the LEM10 and LEM5 groups (16% to 19% for the first 7 nights and 18% to 19% for the last 7 nights) as well as the ZOL and PBO groups (15% to 22% for the first 7 nights and 18% for the last 7 nights). Rates of rebound insomnia were generally lower in the SUNRISE 2 trial and similar between the LEM10 and LEM5 groups based on sSOL measures (11% to 12% for the first 7 nights and 9% to 12% for the last 7 nights) and sWASO measures (12% to 14% for both the first and last 7 nights).

Rates of withdrawal symptoms were similar among the LEM10, LEM5, ZOL, and PBO groups in the SUNRISE 1 trial (10.0%, 11.6%, 14.7%, and 14.1%, respectively) and for the LEM10 and LEM5 groups in the SUNRISE 2 trial (16.8% and 20.7%, respectively).

In both the SUNRISE 1 and SUNRISE 2 trials, suicidal ideation was reported in no more than 3 patients in any treatment group at any postbaseline time point.

Critical Appraisal

Both the SUNRISE 1 and SUNRISE 2 trials appeared to have appropriate methods for blinding to the assigned treatment and randomization with stratification, and adequate power for the primary and secondary outcomes. Adjustments for multiplicity were made for all primary and key secondary outcomes and the type I error was controlled for in both studies. All primary and key secondary outcomes were objective PSG measures (in the SUNRISE 1 trial), or subjective measures based on sleep diary responses (in the SUNRISE 2 trial). The sponsor noted the importance of having objective outcomes to assess the physiological effect of the medication along with subjective outcomes to measure the patient's perception of the medication's effect. According to the clinical expert, PSG results may not always be interpreted meaningfully or consistently when compared side-by-side with subjective or patient-reported outcomes; consequently, they may not be the most meaningful marker of efficacy. The expert further emphasized that insomnia is a subjective issue; therefore, patient-reported outcomes and perceptions of sleep changes may be more appropriate for assessing treatment effect. With all subjective measures, there is risk of bias that cannot be measured and leads to uncertainty of how meaningful the results are. The direction of the treatment effect for objective and subjective measures aligned in the SUNRISE 1 trial, which contributes to the certainty of the results. The numerically higher rates of discontinuations in the LEM10 group compared to the LEM5 group may bias the results, though the magnitude and direction of bias is unknown. There was some missing data at postbaseline visits for all outcomes in either trial, particularly for long-term end points in the SUNRISE 2 study, which prevent strong conclusions from being made. Prespecified subgroup analyses by age were considered exploratory, may not have been powered to detect a treatment difference, were not adjusted for multiplicity, and there was variability in the change from baseline results (noted by large SDs and interquartile ranges). For responder analyses, the SUNRISE 1 study was not powered to detect a treatment difference and neither trial adjusted for multiplicity. As a result of these limitations, conclusions could not be drawn from either the subgroup or responder analysis results.

In general, the clinical expert consulted for this review confirmed that the populations of the SUNRISE 1 and SUNRISE 2 trials were similar to patients seen in Canadian clinics and the trial results would be generalizable with some limitations. There was a large proportion of individuals screened out before randomization, thus producing a study population that may not adequately represent the broader population with people in Canada with insomnia who would otherwise be eligible for treatment with LEM. Eligibility for the SUNRISE 1 study was restricted to females 55 years or older and males 65 years or older and the clinical expert stated that the generalizability of the results would be limited to patients matching these demographics. Further, both the SUNRISE 1 and SUNRISE 2 studies excluded a number of comorbid conditions (e.g., based on Beck Depression Inventory–II and Beck anxiety inventory scores) and had AHI cut-offs that the clinical expert suggested may have captured individuals with insomnia related to mild sleep apnea rather than psychophysiological insomnia. It is uncertain how applicable the trial results would be to patients with the excluded comorbidities or different AHI scores. No dose changes were allowed during the study and it is noted in the Health Canada product monograph that the recommended nightly dose for LEM is 5 mg, which may be increased to 10 mg based on clinical response and tolerability. ZOL was the active comparator in the SUNRISE 1 trial and discussions with the clinical expert and a representative from the Canadian public drug plans indicated that ZOL is not publicly funded by all drug plans in Canada and is less commonly used for the treatment of insomnia; therefore, it is uncertain if it is the most appropriate comparator for a Canadian setting. Patients were required to maintain a sleep diary throughout the course of both studies, and

the clinical expert stated that a sleep diary may not be required in clinical practice. Thus, screening out patients who could not comply with completing a daily sleep diary excluded patients who could be candidates for LEM. Most outcomes identified in the input received by CADTH from patient groups aligned with efficacy and harms outcomes in the studies, though there are still gaps in the evidence for the use of LEM in patients with comorbid conditions and alongside other medications.

Indirect Comparisons

Description of Studies

One sponsor-submitted indirect treatment comparison (ITC) and a published NMA were included. The first, a systematic review and NMA with 11 studies, evaluated the efficacy and safety of LEM in patients with insomnia by comparing it to relevant drugs in Canadian public formularies (e.g., zopiclone, temazepam, triazolam, flurazepam, and nitrazepam) with respect to clinical end points evaluated objectively (by PSG) or subjectively (patient-reported). The clinical end points included LPS, WASO, sleep efficiency, and total sleep time (TST) with subjective assessment in these same end points. Harms related to the use of LEM were also evaluated in an ITC analysis, including treatment discontinuations, somnolence, dizziness, headache, and in a posthoc analysis, risk of falls. The second NMA is a published comparative efficacy analysis aimed at evaluating the efficacy and safety of LEM against other insomnia treatments through a systematic literature review and network meta-analysis. The ITC search strategy included RCTs of drugs used in adults with primary insomnia (not all reimbursed in Canada). The drugs of interest in McElroy et al.'s NMA were LEM, suvorexant, benzodiazepines, Z-drugs (i.e., zolpidem, eszopiclone, zaleplon, zopiclone), trazodone, and ramelteon. Of these, only zolpidem, zopiclone, eszopiclone, trazodone, triazolam, and temazepam were available in the body of evidence from the NMA and of interest to this CADTH reimbursement review.

Efficacy Results

Indirect evidence from the NMAs suggest that for the end point of LPS, LEM5 is superior to triazolam and PBO but no evidence of a difference between LEM5 and LEM10 was observed. With LEM5 as reference, LPS was longer in the PBO group (mean difference of −19.1 minutes; 95% CI, −3.20 minutes to −35.0 minutes, in which a negative value in the mean difference implies improvement in favour of LEM5). Patients treated with LEM5 had a reduction in LPS when compared to triazolam of 0.5 mg (mean difference of −34.1 minutes; 95% CI, −5.47 minutes to −62.8 minutes). The results for LEM10 were consistent with LEM5. In the second NMA, LEM showed a reduction in LPS when compared to placebo (−18.6 minutes; 95% credible interval [CrI], −29.0 minutes to −10.9 minutes), zolpidem-ER (−13.4 minutes; 95% CrI, −24.4 minutes to −4.9 minutes), and triazolam (−23.2 minutes; 95% CrI, −38.8 minutes to −9.6 minutes).

For the end point of WASO, the evidence suggests LEM5 and LEM10 were superior to PBO, but the evidence against triazolam was imprecise to detect a difference in PSG-assessed WASO between LEM5, LEM10, and triazolam 0.5 mg. In the second NMA, for WASO, LEM was superior to placebo and ZOL immediate-release, with an average reduction of 21.3 minutes (95% CrI, −29.6 minutes to −10.1 minutes) and 19.6 minutes (95% CrI, −31.9 minutes to −0.3 minutes), respectively.

For the evaluation of objectively measured sleep efficiency, LEM5, LEM10, flurazepam 30 mg, and triazolam 0.5 mg were compared in the NMA. The mean differences in sleep efficiency

for LEM5 and LEM10 compared with PBO were 7.62% (95% CI, 5.93 to 9.31%) and 8.80% (95% CI, 10.5 to 7.06%), respectively (where higher values mean improvement in favour of LEM). The mean differences in sleep efficiency for LEM5 and LEM10 compared with triazolam were 9.62% (95% CI, 14.3 to 4.92%) and 10.8% (95% CI, 15.5 to 6.09%), respectively. Effect estimates for the comparisons between LEM5 and LEM10 and flurazepam were too imprecise to draw a conclusion.

TST data were only available for LEM5 and LEM10 against PBO. The NMA showed that effect estimates were imprecise to detect a difference between LEM5 and LEM10 (−4.65 minutes; 95% CI, −2.45 minutes to 11.8 minutes). Although relative to PBO, LEM5 and LEM10 were associated with an improvement of 34.8 minutes (95% CI, 27.4 minutes to 42.4 minutes) and 39.5 minutes (95% CI, 32.1 minutes to 46.9 minutes), respectively.

In the second NMA, for the subjective outcomes, LEM was superior to placebo in all end points evaluated but not against eszopiclone for the subjective quality of sleep end point (mean difference of −0.6; 95% CrI, −0.9 to −0.2). For the rest of comparisons, no evidence of effect was observed.

Harms Results

The evidence from the ITC suggested that LEM10 had an increased risk of drug discontinuation when compared to LEM5 (odds ratio [OR] = 1.99; 95% CI, 1.06 to 3.74) and PBO, but not against the other comparators. The odds of discontinuations were less for PBO compared with LEM10 (OR = 0.48; 95% CI, 0.25 to 0.91). The effect estimates for all other comparisons with LEM10 were too imprecise to draw a conclusion.

For the end point of somnolence, when compared with LEM 5, PBO had reduced odds of somnolence (OR = 0.25; 95% CI, 0.12 to 0.52); similarly, the odds were reduced in the triazolam 0.25 mg (OR = 0.31; 95% CI, 0.14 to 0.69) and zopiclone arms. Increased odds of somnolence for LEM10 were observed against PBO, triazolam 0.25 mg, and zopiclone 7.5 mg. For other comparisons (i.e., LEM5 and LEM10 versus flurazepam, temazepam, and triazolam 0.125 mg), the effect estimates were too imprecise to detect a difference.

For the end point of dizziness, the effect estimates were too imprecise to draw conclusions about the effect of LEM5 or LEM10 compared with PBO, flurazepam, triazolam, or zopiclone.

For the end point of headache, the results were also too imprecise to detect a difference in the odds between LEM5 and each of the alternatives. This situation also occurred in the comparison of LEM10 to the other comparators.

In an additional posthoc analysis (Bucher ITCs) of studies reporting falls, using LEM5 as the reference, no evidence of any difference could be detected when comparing to those receiving triazolam, flurazepam, lorazepam, trazodone, benzodiazepines, and Z-drugs due to the high imprecision of the results. When LEM10 was used as the reference, the odds of falls were higher with triazolam, flurazepam, and lorazepam. When the entire class of benzodiazepines and trazodone were compared to LEM10, the odds of falls were also higher with the former drugs. Even though these findings suggested that LEM10 is associated with a reduction in the odds of falls when compared to other drugs, the results are very imprecise, with wide CIs to draw conclusions.

In the second NMA evaluated in this CADTH report, there was no evidence of increased or decreased odds for presenting SAEs for patients receiving LEM when compared to relevant

comparators, mainly due to wide CrIs. Similarly, no difference was observed in the odds of withdrawals due to AEs or in the odds of falls. LEM was associated with lower odds of dizziness compared with ZOL immediate-release, ZOL extended-release, and eszopiclone. LEM, however, increased the odds of somnolence when compared to placebo, zolpidem, and eszopiclone.

Critical Appraisal

The results from both NMAs have uncertainty due to risk of bias in the individual studies (i.e., unclear randomization, allocation concealment, baseline imbalances), heterogeneity in the pairwise comparisons, and suspected publication bias. Furthermore, the evidence is imprecise in most of the effect estimates from both NMAs, with wide CIs that could include an appreciable threshold of benefit or harm. In the NMAs, there were concerns of incomplete information and discrepancies in the included studies that could affect the plausibility of the transitivity assumption. Overall, the populations included in the individual studies of the network are generalizable to the population of people in Canada without comorbid conditions.

Other Relevant Evidence

Description of Studies

Study 312 was an open-label, phase IIIb, pilot, multicentre trial (N = 53) investigating next-dose transition from ZOL to LEM for the treatment of insomnia. The trial included adult patients with insomnia who were receiving ZOL as monotherapy, and who agreed to substitute it with LEM.

Efficacy Results

Overall, 81.1% of patients successfully transitioned to LEM at the end of the 2-week titration period and entered the extension phase. A total of 15 (48.4%) patients had a LEM dose increase from 5 mg to 10 mg, while 5 (22.7%) patients had a LEM dose decrease from 10 mg to 5 mg at the end of the 2-week titration period.

At the end of the titration period, patients in both the LEM5 and LEM10 groups indicated that LEM had a positive effect on sleep, time to fall asleep, and TST. A large proportion of patients felt that the medication was "too weak." In the overall trial population, the mean change in ISI total score was −4.6 (SD = 6.26) and the mean change in quality of sleep score was −0.19 (SD = 0.92) at the end of the titration period.

In the overall trial population, at baseline and at the end of the titration period, the mean sleep efficiency scores were 79.03% (SD = 85.4%) and 80.17% (SD = 8.49%), respectively; the mean WASO scores were 80.90 minutes (SD = 33.23 minutes) and 83.92 minutes (SD = 35.44 minutes), respectively; and the mean TST scores were 403.44 minutes (SD = 62.07 minutes) and 412.11 minutes (SD = 60.17 minutes), respectively.

Harms Results

Of the 53 patients enrolled in the core study, 20 (37.7%) experienced at least 1 TEAE (5 patients from the LEM5 group and 15 patients from the LEM10 group). The most common TEAEs were abnormal dreams (7.5%) and somnolence (7.5%). In the overall trial population, 13% of patients withdrew from treatment due to an AE. No deaths or SAEs leading to study drug discontinuation were reported in the study.

Critical Appraisal

Study 312 had an open-label design, small sample size, short study duration, no formal statistical testing, subjective secondary end points, 50% screening failures, and chose ZOL as the previous treatment to transition from (rather than other treatments that may have been more relevant to Canadian clinical practice), which prevent conclusions from being drawn and limits generalizability to the population of people in Canada with insomnia.

Economic Evidence

Table 1: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Decision-tree model
Target population	Patients with insomnia that is characterized by difficulties with sleep onset and/or sleep maintenance
Treatment	Lemborexant
Dose regimen	5 mg to 10 mg once daily, depending on clinical response and tolerability
Submitted price	Lemborexant 5 mg and 10 mg: $1.5198 per tablet
Treatment cost	The annual cost of lemborexant was $555 per patient.
Comparators	• Benzodiazepines (flurazepam, lorazepam, nitrazepam, triazolam, temazepam) • A Z-drug (zopiclone) • An antidepressant (trazodone) • An antipsychotic (quetiapine) • No treatment
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	6 months
Key data source	• Clinical efficacy for lemborexant and no treatment: SUNRISE-1 and SUNRISE-2; comparative efficacy with active comparators: sponsor-submitted network meta-analysis • Safety (i.e., falls, MVAs, and WPAs): literature reviews, clinical expert assumptions, and indirect comparisons
Key limitations	• The sponsor did not consider comparators that the clinical expert consulted by CADTH deemed relevant in clinical practice in Canada, such as doxepin and mirtazapine. The cost-effectiveness of lemborexant compared to the missing comparators is unknown. • The comparative clinical effects of lemborexant (in terms of response based on sSOL) relative to other active comparators is highly uncertain. The indirect treatment comparison evidence was absent for flurazepam, lorazepam, nitrazepam, zopiclone, trazodone, and quetiapine, and uncertain for triazolam and temazepam. As such, no firm conclusions about the comparative efficacy based on sSOL can be drawn. • There is no evidence to model the impact of insomnia treatment on the risk of MVAs and WPAs. The sponsor's approach to estimating the odds of MVAs associated with each active comparator (odds ratio = 2.20) was based on the assumption that an intoxicated person is at the same risk of an MVA as a

Component	Description
	person with insomnia, which is unlikely to be a valid estimation of the risk of MVAs or WPAs associated with insomnia treatments. • The impact of insomnia treatments on the risk falls is highly uncertain, due to the absence of direct evidence and imprecision in the indirect estimates. • The sponsor considered both a disutility for insomnia for patients not responding to treatment and a disutility associated with treatments, which included somnolence and dizziness. These additive disutilities likely resulted in double counting, and the additive use of these disutilities favoured lemborexant by overestimating the QALY decrement with active comparators. • The sponsor assumed that a higher number of primary care visits is incurred by patients who are untreated. The clinical expert noted that it is unlikely that the number of primary care visits would differ from that of patients receiving treatment.
CADTH reanalysis results	• To account for the key limitations identified, CADTH assumed no difference in the risk of falls, MVAs, WPAs, and the number of additional physician visits among treatments; treatment disutilities, such as somnolence and dizziness, were also excluded. • In the CADTH base case, only 2 treatments were considered optimal (on the cost-effectiveness frontier): trazadone and lemborexant. All other comparators were dominated (more costly and less effective) by trazadone. The ICER for lemborexant compared to trazodone was $76,941 per QALY gained (incremental costs = $229; incremental QALYs = 0.003). • The interpretation of the CADTH base case is limited by the comparative clinical information. CADTH could not account for the uncertainty in the response rate of lemborexant compared to other active comparators. Given the limitations of the clinical evidence, and small differences in QALYs among treatments, there is likely no evidence to suggest that lemborexant warrants a price premium compared to other treatments.

ICER = incremental cost-effectiveness ratio; MVA = motor vehicle accident QALY = quality-adjusted life-year; sSOL = subjective sleep onset latency; WPA = workplace accident.

Budget Impact

CADTH identified the several key limitations with the sponsor's analysis. The number of eligible patients was underestimated because the proportion of claims indicated for insomnia was underestimated. Furthermore, the market share of LEM was underestimated given its potential use as first-line treatment. Finally, the treatment cost of comparators was not aligned with costs used in the cost-utility analysis and overestimated in the budget impact analysis.

CADTH corrected the treatment cost of comparators by aligning them with the cost-utility analysis. CADTH reanalysis included revising the proportion of claims indicated for insomnia based on feedback from the clinical expert and assuming a higher market share of LEM. Based on CADTH reanalysis, the budget impact to the public drug plans of introducing LEM is expected to be $20,602,763 in year 1, $28,099,123 in year 2, and $41,080,131 in year 3, for a 3-year total of $89,782,016.

Request for Reconsideration

The sponsor filed a request for reconsideration for the draft recommendation for LEM for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. In their request, the sponsor identified the following issues:

- The sponsor is of the view that the safety profile of LEM has been well studied, unlike current publicly reimbursed treatments used for insomnia, and was established through 2 phase III RCTs, including for 12-months of treatment in the SUNRISE-2 trial. The sponsor provided data from a PSUR.
- The sponsor is of the view that the results of the LEM clinical program are consistent and clinically meaningful and are aligned with patient values. The sponsor included an unpublished manuscript by Drake et al. (2021) that provided additional evidence from posthoc analyses for LEM's efficacy by the PGI-Insomnia in the SUNRISE 2 trial.
- The sponsor is of the view that, given the totality of evidence for LEM, LEM is the most effective option compared with publicly reimbursed options. The sponsor indicated that this is supported by multiple indirect comparisons, including a recent independent systematic review and NMA reported by De Crescenzo et al. (2022), which compared LEM to other pharmacological treatment for the acute and long-term treatment of adults with insomnia. The sponsor is of the view that LEM provides an additional effective option without any of the signals that it is associated with similar safety concerns of current publicly reimbursed treatments.
- The sponsor is of the view that the patient populations in the SUNRISE trials were similar to patients seen in Canadian clinics; therefore, the trial results are generalizable to patients in Canada. The sponsor reported that patients with moderate to severe comorbid conditions, such as moderate to severe sleep apnea, depression, and anxiety, were excluded as they would need different treatments for those conditions, allowing the clinical program to focus on patients meeting criteria for chronic insomnia.

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

- feedback from the sponsor
- information from the initial submission relating to issues identified by the sponsor
- feedback from a clinical specialist with expertise in the diagnosis and management of insomnia
- feedback from the public drug plans
- feedback from 2 clinician groups: the National Advisory Board and the CCSSP
- feedback from 3 patient groups: Menopause Chicks, Migraine Canada, and the MDSC.

All stakeholder feedback received in response to the draft recommendation from patient and clinician groups and the public drug programs is available on the CADTH website.

Clinical Evidence for the Reconsideration

Drake et al. (2021)

In the request for reconsideration, the sponsor submitted an unpublished manuscript by Drake et al. (2021) to provide evidence for LEM's efficacy by the PGI-I in the SUNRISE 2 account. Posthoc analyses were conducted to examine the possible relationships between

the PGI-I items and ISI items to assess patients' perceptions of medication efficacy as well as between item 4 of the PGI-I (appropriateness of medication strength) and TEAEs.

Patients who responded positively to items 2 (time to fall asleep) and 3 (TST) of PGI-I generally showed larger magnitudes of improvement in sSOL and subjective TST. Patients who responded that the medication strength (item 4) was "just right" showed greater improvements in sSOL, sWASO, and subjective TST compared to the other responses. Patients who indicated a positive response to items 1 to 3 had the greatest mean change from baseline for the modified ISI score (i.e., item 5 removed). The authors concluded that the results suggest improvements with LEM and consistency among different measurements.

The PGI-I and ISI were exploratory and secondary outcomes, respectively, in the SUNRISE 2 trial, and neither was controlled for increased risk of type I error. SUNRISE 2 was not designed to show relationships between sleep measurements, and this limits the confidence in the posthoc analyses results. Wide ranges, large SDs, and wide quartile ranges indicated variability in the results. Internal consistency was assessed for modified ISI scores, though no other psychometric properties were assessed.

Periodic Safety Update Report (2022)

In the request for reconsideration, the sponsor provided a PSUR, which includes aggregate data from approximately 4,024 adult patients with insomnia disorder, irregular sleep-wake rhythm disorder, or healthy volunteers have been enrolled in the LEM clinical development program. In total, 2,641 received LEM, 990 received placebo, and 393 received a benzodiazepine receptor agonist (i.e., zolpidem, eszopiclone, brotizolam, or flunitrazepam); patients may have received more than 1 medication.

Key safety concerns were identified and reported for the total population treated (patients with insomnia, irregular sleep-wake rhythm disorder, or healthy volunteers). There was no "significant new information" identified for daytime impairment or somnolence. [redacted]

The indication for LEM under review includes patients with insomnia. The aggregated data in the PSUR make it difficult to attribute safety signals to only patients with insomnia.

Indirect Evidence

In the request for reconsideration, the sponsor provided new indirect evidence from De Crescenzo et al. (2022). The objective of the work conducted by De Crescenzo et al. was to conduct a systematic review and NMA to inform clinical practice by comparing different pharmacological treatments for the acute and long-term treatment of adults with insomnia.

The primary efficacy outcome was sleep quality or satisfaction as measured by any self-reported scale, such as the Pittsburgh Sleep Quality Index, ISI, or Leeds Sleep Evaluation Questionnaire. Indirect evidence from the NMAs suggest that LEM was superior to placebo in both the short term and long term, but inferior to short-acting and intermediate-acting

benzodiazepines, as a class, in the short-term analysis. All other comparisons with LEM were inconclusive due to wide 95% CIs that included the null effect. Based on the Confidence in Network Meta-Analysis (CINeMA) tool, the comparison of LEM versus placebo in short-term efficacy was associated with a "moderate" degree of certainty, and in long-term efficacy was associated with a "very low" degree of certainty. The comparisons between LEM and short- and intermediate-acting benzodiazepines were associated with "moderate" and "low" degrees of certainty, respectively.

No results for the outcome of tolerability (i.e., dropouts due to AE) were conclusive for the outcome of tolerability. Results for the outcome of safety (i.e., patients who experienced at least 1 AE) suggested that LEM was superior to short- and long-acting benzodiazepines, as a class, with a "low" degree of certainty based on CINeMA. For the rest of the available comparisons, including zopiclone, the evidence was inconclusive due to wide 95% CIs that included the null effect.

The published NMA by De Crescenzo et al. (2022) assessed the efficacy and harms of a comprehensive list of active pharmacological treatments for adults with insomnia disorder as evaluated in double-blind RCTs. Some of the included pharmacological treatments were relevant to the Canadian landscape, including zopiclone. Overall, this NMA was more comprehensive but had similar methodological limitations to the 2 NMAs included in the initial submission to CADTH.

CDEC Information

Initial Meeting Date: July 28, 2022

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Regrets: Two expert committee members did not attend.

Conflicts of interest: None.

Reconsideration Meeting Date: December 21, 2022

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Peter Zed, and Mr. Morris Joseph.

Regrets: One expert committee member did not attend.

Conflicts of interest: None.