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Drug Class Update with New Drug Evaluation: Sedatives

Date of Review: August 2022

Generic Name: daridorexant

Date of Last Review: December 2020
Dates of Literature Search: 04/01/2020 – 03/14/2022
Brand Name (Manufacturer): Quviviq (Idorsia Pharmaceuticals US Inc.)
Dossier Received: no

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary

- Is there any new evidence that would change the current policy for medicines to treat sleep disorders?
- The American Academy of Sleep Medicine and the European Sleep Research Society recommend cognitive behavioral therapy (CBT) for sleep disorders:
  - that make it difficult to fall asleep or stay asleep *and*
  - where lack of sleep creates difficulty doing activities during the day.
- Providers can prescribe medicines for sleep disorders when cognitive behavioral therapy does not improve patient sleep.
  - Many medicines are used for sleep disorders.
  - Studies show that, when used for less than 3 months, these medicines likely have the same benefits and risks.
  - When patients use these medicines for more than 3 months, the risk of bone fracture and dementia may increase.
  - Risk of side effects may increase as people get older, particularly if over 65 years of age.
- Daridorexant is a new medicine the Food and Drug Administration (FDA) approved for sleep disorders in adults. Two 3-month studies showed that the medicine helped people fall asleep about 8-12 minutes faster than without medicine. And, if patients woke up during the night, the medicine reduced how long they stayed wake by about 10-18 minutes.
- Providers must explain to the Oregon Health Authority why someone needs a sedative before Medicaid will pay for it. This process is called prior authorization.
- Medicaid Open Card will pay for melatonin when prescribed for children but does not require prior authorization. Melatonin is not covered for adults.
- The Mental Health Clinical Advisory Group (MHCAG) recently posted guidance on how to stop taking benzodiazepines safely. The Drug Use Research Management program and the Pharmacy and Therapeutics Committee recommend policy updates to match this guidance.

Purpose for Class Update:
To evaluate new updated evidence for the sedative class and place in therapy for a new drug, daridorexant (Quviviq), recently approved by the Food and Drug Administration (FDA).

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Research Questions:

1. What is the comparative evidence of efficacy or harms between sedatives when used for treatment of sleep disorders?
2. Are sedatives more effective or associated with more harms than no treatment when used to treat sleep disorders?
3. Are there subgroups of patients based on specific demographics, co-morbidities or other factors (e.g., age, co-morbid behavioral or mental disorders, concomitant medications, etc.) in which one sedative is more effective or associated with fewer adverse events than another sedative?

Conclusions:

- Two high-quality systematic reviews, one expanded indication, and one new drug approval were identified since the last drug class update.
- A systematic review evaluating use of melatonin for sleep disorders in adults who are blind found insufficient evidence for efficacy and safety of melatonin.[1]
- A systematic review evaluating sleep disturbances in patients with dementia identified low quality evidence that trazodone 50 mg may improve sleep efficiency and total sleep time (mean difference [MD] 42.46 minutes, 95% confidence interval [CI] 0.9 to 84.0) with short-term treatment (2 weeks).[2] Orexin antagonists (suvorexant or lemborexant) may improve total sleep time (MD 28.2 minutes, 95% CI 11.1 to 45.3) and wake after sleep onset times (MD –15.7 minutes, 95% CI –28.1 to –3.3) compared to placebo over 4 weeks of treatment (based on moderate quality evidence).[2] Other sleep outcomes demonstrated no difference from placebo. Ramelteon and melatonin did not demonstrate any change in sleep outcomes based on low quality evidence.[2] No studies evaluated other commonly prescribed therapies such as benzodiazepines or benzodiazepine receptor agonists (e.g., eszopiclone, zolpidem, zaleplon).
- Daridorexant, an orexin receptor antagonist, was FDA approved in January 2022 for the treatment of insomnia in adults. Treatment was evaluated over 3 months in 2 phase 3 RCTs which demonstrated improvement in time awake after sleep onset (WASO) and latency to persistent sleep (LPS) compared to placebo (moderate quality evidence).[3] At 3 months, WASO improved by an average of 18 minutes compared to placebo with a 50 mg dose and 10-12 minutes with a 25 mg dose.[3] LPS improved by about 12 minutes with a 50 mg dose and 8-9 minutes with a 25 mg dose.[3] Though population level averages cannot be directly applied to individual patients, these changes likely represent only a marginal clinical improvement for many patients based values of minimum clinically important differences (MCIDs) referenced in the literature (WASO of 20 minutes, LPS of 10 minutes). Patients with comorbid disorders were excluded from these studies and patient demographics other than White patients were underrepresented. Subgroup analyses based on age and gender demonstrated similar direction of effect.[3]
- There is insufficient evidence comparing daridorexant to other drugs for insomnia. Direct comparative data includes only a small phase 2 trial.[4]
- Tasimelteon oral suspension, was FDA approved in December 2020 for nighttime sleep disturbances in Smith-Magenis Syndrome in patients at least 16 years of age based on results from one small, crossover, placebo-controlled trial (n=25).[5]
- Patient and provider resources describing best practices for benzodiazepine tapers were recently published by the Oregon Health Authority Mental Health Clinical Advisory Group (MHCAG).[6] Guidance recommends that taper schedules be individualized, and many patients may benefit in switching to a longer-acting benzodiazepine like diazepam before tapering.[6]

Recommendations:

- No policy changes recommended based on clinical evidence. After evaluation of costs in executive session, no PDL changes were recommended.
- Update prior authorization (PA) criteria to facilitate benzodiazepine tapers as described in recent guidance from the mental health clinical advisory group.

Summary of Prior Reviews and Current Policy

- There is insufficient comparative evidence that assesses differences in efficacy or effectiveness between sedative classes or between individual sedative agents. Similar improvement in total sleep time was found with short-term use of benzodiazepines, non-benzodiazepine sedatives, and sedating antidepressants compared to placebo based on moderate-quality evidence.[7]
- In elderly patients over 65 years of age, there is evidence supporting use of eszopiclone to improve total sleep time and wake time after sleep onset, use of zolpidem and ramelteon to improve sleep onset latency, and doxepin to improve insomnia symptoms.
- There is insufficient evidence to assess efficacy or safety of long-term use of sedatives.[7]
    - Few randomized control trials for non-benzodiazepine sedatives examine outcomes beyond 3 months, and study durations of benzodiazepines beyond 14 days were rare.
    - Evidence from observational studies indicates long-term sedative use may be associated with increased risk of fractures and dementia. The risk of fracture may depended on the length of time people used the drugs, with new users of these drugs at greatest risk of hip fracture.[7] FDA labeling for non-benzodiazepine sedatives includes warnings for risk of rare but serious adverse effects including daytime memory and psychomotor impairment, abnormal thinking and behavior changes, parasomnias (such as sleep paralysis), complex behaviors (such as sleep driving), depression, and suicidal thoughts and actions.
- There is also insufficient evidence to compare efficacy of tapering regimens to improve rates of sedative discontinuation. Interventions to improve patient education and increase psychosocial support have improved rates of benzodiazepines discontinuation when used in combination with tapering strategies.
- Cognitive Behavioral Therapy (CBT) is highly recommended as first-line therapy for chronic insomnia by both the American Academy of Sleep Medicine[8] and the European Sleep Research Society[9] based on high-quality evidence. A sedative can be offered if CBT is not effective or not available.[8,9] Orexin receptor antagonists (suvorexant), benzodiazepines (triazolam and temazepam only), benzodiazepine receptor agonists (eszopiclone, zaleplon, zolpidem), doxepin, and ramelteon are all weakly recommended to treat sleep onset and/or sleep maintenance insomnia based on low-quality evidence.[8] However, long-term treatment of chronic insomnia with a sedative is not recommended because of lack of evidence and possible adverse effects based on low-quality evidence.[9] Trazodone, and diphenhydramine are not recommended due to adverse effects and lack of efficacy, and there is insufficient evidence for use of melatonin in adults.[8]
- Uncomplicated sleep disorders (including insomnia) are unfunded conditions on the prioritized list unless the sleep disorder exacerbates or worsens a concomitant funded condition. All drugs currently require prior authorization for this class except melatonin in children. Melatonin coverage for patients less than or equal to 18 years of age was added as a preferred agent in October 2021. The current prior authorization policy restricts use of concomitant use of benzodiazepines, opioids or sedatives.

Background:

Sleep disorders encompass a wide variety of conditions including insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, and sleep-related movement disorders.[10] This review will focus primarily medications listed in the Sedative PDL class (see **Appendix 1**) for treatment of insomnia, one of the most common sleep disorders. Other disorders are discussed only briefly. Drugs not covered in this review include lorazepam, sodium oxybate, barbiturates, sedating antidepressants or atypical antipsychotics. Some of these medications are addressed in other class reviews and are covered with other PA criteria. For example, lorazepam is included in PA criteria for the benzodiazepine class, and current PA criteria restrict use of low-dose quetiapine for insomnia.

Insomnia is defined as the subjective perception of difficulty with sleep which occurs despite adequate opportunity for sleep and causes functional impairment during the day.[8,11] Insomnia is often classified as short-term (typically <3 months in duration with an identifiable stressor), long-term (occurring ≥3 times per

week for >3 months) or other (if criteria for short- and long-term criteria are not met). Diagnosis is primarily based on sleep history.[10,11] It is estimated that up to 30-50% of the population experience insomnia symptoms, and chronic insomnia is diagnosed in approximately 5-10% of patients.[8] Insomnia is more common in elderly, females, individuals who are divorced or separated, those with shift work, and patients with lower socioeconomic status.[12] Insomnia symptoms have been associated with reduced health-related quality of life and cognitive decline in patients over 65 years of age.[12] Insomnia can also worsen outcomes for patients with comorbid conditions including cardiovascular disease, post-traumatic stress disorder, and depression.[12] Insomnia may also be associated with a wide variety of comorbid conditions, both medical and psychological. Identification and treatment of contributing factors and comorbid conditions (such as medical conditions, substance misuse and psychiatric conditions) is important for the management of insomnia symptoms.[11]

Cognitive Behavioral Therapy (CBT) is recommended as first-line therapy for chronic insomnia by both the American Academy of Sleep Medicine[8] and the European Sleep Research Society[9] based on high-quality evidence. A sedative can be offered if CBT is not effective or not available.[8,9] Evidence supports efficacy of both brief CBT interventions and longer therapy.[9] Orexin receptor antagonists (suvorexant), benzodiazepines (triazolam and temazepam only), benzodiazepine receptor agonists (eszopiclone, zaleplon, zolpidem), doxepin, and ramelteon all have weak recommendations to treat sleep onset and/or sleep maintenance insomnia based on low-quality evidence.[8] However, long-term treatment of chronic insomnia with a sedative (≥12 weeks) is not recommended because of lack of evidence and possible adverse effects based on low-quality evidence.[9] FDA labeling for most sedative drugs indicated for insomnia recommends re-evaluation of comorbid diagnoses which could be contributing to symptoms if insomnia persists for more than 7-10 days of treatment. Trazodone, and diphenhydramine are not recommended due to adverse effects and lack of efficacy, and there is insufficient evidence for use of melatonin in adults.[8]

Common adverse effects associated with sedative medications include dizziness, daytime drowsiness, and somnolence. Evidence from observational studies indicates long-term sedative use may be associated with increased risk of fractures and dementia. The risk of fracture may depended on the length of time people used the drugs, with new users of these drugs at greatest risk of hip fracture.[7] FDA labeling for non-benzodiazepine sedatives includes warnings for risk of rare but serious adverse effects including daytime memory and psychomotor impairment, abnormal thinking and behavior changes, parasomnias (such as sleep paralysis), complex behaviors (such as sleep driving), depression, and suicidal thoughts and actions. Risk for daytime impairment may be higher in women or elderly who metabolize and eliminate sedative medications more slowly from the body.[13] The FDA warns that high levels of a sedative in the bloodstream can result in impairment even if patients feel fully awake.[13] Benzodiazepine sedatives are also associated with physical dependence and a taper plan is usually recommended to minimize withdrawal symptoms and facilitate discontinuation after routine, long-term use. Provider resources and best practices for benzodiazepine tapers were recently published by the Oregon Health Authority Mental Health Clinical Advisory Group (MHCAG).[6] Taper schedules be individualized based on patient circumstances, diagnoses, dose, and length of benzodiazepine use. Many patients may benefit in switching, or cross-tapering, to a longer-acting benzodiazepine like diazepam before reducing their total benzodiazepine dose.[6]

Improvement in symptom severity is typically measured by patient-reported improvement in severity, sleep symptoms, and quality of life. However, differences in efficacy are often difficult to evaluate due to a strong placebo response which is apparent with both subjective and objective measures of efficacy. One systematic review examining effect size of the placebo response in RCTs of sedative drugs for treatment of primary insomnia determined that approximately 64% of drug response could be attributed to a placebo effect.[14] Sleep outcomes which are commonly reported in trials include subjective change in sleep latency, total sleep time, wake time after sleep onset, sleep efficiency, and sleep quality. Change in these outcome measures compared to placebo which may represent clinically meaningful improvement have been proposed by the American Academy of Sleep Medicine (**Table 1**). Other assessment scales include the Insomnia Severity Index (ISI) or the Pittsburgh Sleep Quality Index (PSQI) which document overall symptom severity.[15]

Table 1. Clinically Meaningful Outcomes for Chronic Insomnia (Adapted from the American Academy of Sleep Medicine).[8]

Outcome (units)	Minimum Clinically Important Difference Versus Placebo^		
	Polysomnography (PSG)	Actigraphy	Subjective
Sleep Onset Latency (min)	10	10	20
Total Sleep Time (min)	20	20	30
Wake After Sleep Onset (min)	20	20	30
Quality of Sleep (varies*)	Varies	Varies	Varies
Sleep Efficiency (%)	5	5	10
Number of Awakenings (n)	2	2	0.5

^Clinical significance was judged to be present when a specific agent led to a mean change in the outcome of this magnitude, compared to placebo.
*For standardized mean difference (SMD), an effect size of 0.5 is considered clinically significant.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Pharmacotherapies for sleep disturbances in dementia
A Cochrane systematic review on pharmacotherapy for sleep disturbances in patients with dementia was published in 2020.[2] Identified trials evaluated treatment with melatonin (n=222), trazodone (n=30), ramelteon (n=74), or an orexin receptor antagonist (suvorexant or lemborexant; n=323). Primary outcomes included objective sleep measures evaluated by polysomnography or actigraphy (such as total sleep time, sleep latency, nocturnal awakenings, etc) and were evaluated over short-term (≤ 6weeks) and long-term therapy (> 6 weeks).[2] For patients with moderate to severe Alzheimer's dementia, trazodone 50 mg may improve sleep efficiency (MD 8.53%, 95% CI 1.9 to 15.1) and total sleep time (MD 42.46 minutes, 95% CI 0.9 to 84.0) over 2 weeks compared to placebo (low quality evidence).[2] Other sleep outcomes and outcomes for cognitive function failed to achieve statistical significance and were limited by significant imprecision.[2] In patients with mild to moderate Alzheimer's dementia, orexin antagonists (suvorexant or lemborexant) may improve total sleep time (MD 28.2 minutes, 95% CI 11.1 to 45.3) and wake after sleep onset times (MD –15.7 minutes, 95% CI –28.1 to –3.3) compared to placebo over 4 weeks of treatment (moderate quality evidence).[2] There was no difference in number of nocturnal awakenings, change in cognitive function, or caregiver distress based on moderate quality evidence. Ramelteon did not improve sleep outcomes in one phase 2 trial in patients with mild to moderate Alzheimer's dementia (low quality evidence).[2] Trials evaluating up to 10 mg of melatonin were mostly conducted in patients with moderate to severe Alzheimer's dementia and identified no improvement in total sleep time or the ratio of day-time to night-time sleep (low quality evidence).[2] Similarly, there was no difference on sleep efficiency, time awake after sleep onset, number of night-time awakenings, cognitive function, or caregiver burden (low quality evidence).[2] Serious adverse events were rarely reported for all treatments.

Melatonin for treating sleep disorders in adults who are blind

An evidence review was developed by NICE 2021 evaluating use of melatonin for treatment of sleep disorders in adults who are blind.[1] Only one RCT was included in the analysis; other identified trials were crossover studies without adequately reported randomization methods which may increase risk of bias.[1] All studies were small (with the largest enrolling 13 participants) and were likely underpowered to determine differences between groups.[1] All identified studies were of short duration (maximum 12 weeks) with long-term efficacy and safety unknown.[1] Overall, 2 studies (n=20) found no significant improvement in total sleep time with 2mg or 10mg of melatonin. One study reported a statistically significant improvement in total sleep time of 0.65 hours (about 40 minutes) with use of melatonin 0.5 mg compared to placebo.[1] Two studies reported melatonin decreased the time spent awake after sleep onset by 0.56 hours with melatonin 0.5mg and 1.3 hours with melatonin 10 mg.[1] No studies identified a difference with melatonin compared to placebo for sleep latency or quality of life. Overall, authors concluded that evidence is insufficient to determine efficacy and safety for use of melatonin in adults who are blind.[1]

After review, 11 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses),[16-27] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled),[23,25,26] or outcome studied (e.g., non-clinical).

New Guidelines:

No high-quality guidelines were identified.

New Formulations or Indications:

A new formulation of tasimelteon (Hetlioz LQ™), an oral suspension, was FDA approved in December 2020.[5] Tasimelteon was previously available as a capsule for non-24 hour sleep-wake cycle disorder. Tasimelteon also received an expanded indication for nighttime sleep disturbances in Smith-Magenis Syndrome in patients at least 16 years of age.[5] Smith-Magenis Syndrome is a rare developmental disorder which affects multiple organ systems and is often associated with multiple behavioral health conditions including intellectual disability, speech and motor delays, sleep disturbances, and self-injurious behaviors.[28] It is most commonly caused by a deletion in chromosome 17 and is estimated to affect 1 in 15,000-25,000 patients.[28] The recommended dose in pediatric patients less than 28 kg is weight based at 0.7 mg/kg one hour before bedtime.[5] Approval was based on a single 9-week double-blind, placebo-controlled, crossover RCT including 25 patients (age 3-39 years) with Smith-Magenis Syndrome and sleep disturbances.[5] Patients were randomized to receive tasimelteon or placebo for 4 weeks, had a 1 week washout period, then received the alternative medication for 4 weeks. The primary outcomes were subjective total sleep time and nighttime sleep quality (reported by the patient's parent/guardian) for the 50% of nights with the worst sleep.[5] Sleep quality was rated on a 5 point scale from excellent (5) to poor (1). Compared to placebo, tasimelteon treatment resulted in improved sleep quality for the 50% of nights with the worst sleep quality though magnitude of benefit was small (2.8 vs. 2.4; least square mean difference 0.4 [95% CI 0.1 to 0.7]).[5] The difference from placebo in total sleep time for the 50% of nights with the worst sleep was not statistically improved with tasimelteon (7 vs. 6.7 hours; least square mean difference 0.3 [95% CI -0.0 to 0.6]).[5]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month/Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Zolpidem[29]	Ambien®	2/2022	Warnings/Precautions	**Abnormal Thinking and Behavioral Changes:** Addition of delirium to warning/precautions of zolpidem based on post-marketing reports. **Respiratory Depression:** Strengthen warnings to emphasize risk with concomitant use of opioids or other central nervous system depressants

Temazepam[30]	Restoril™	2/2021	Box Warning Warnings/Precautions	Language in labeling revised to emphasize risk of abuse, misuse, addiction, dependence, and withdrawal symptoms. Use of benzodiazepines exposes patients to risk of abuse, misuse, and addiction. Before and throughout prescribing, assess a patient's risk for abuse or misuse. Long-term use can increase risk of physical dependence with risk of withdrawal symptoms upon discontinuation or with rapid tapering. Gradual tapers may decrease risk of withdrawal symptoms.

Randomized Controlled Trials:
A total of 93 citations were manually reviewed from the initial literature search. After further review, all but 2 RCTs were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Castro, et al. 2020.[31] N=67 DB, double-dummy, RCT Duration: 3 months	1. Oral zolpidem 10 mg, nightly 2. Sublingual zolpidem 5mg nightly with 5mg as needed	Adults with insomnia diagnosis and self-reported nocturnal awakenings	Sleep onset latency, Nights with middle of the night awakenings	Change in sleep onset latency 1. +10 minutes (SD 29) 2. -14 minutes (SD 42) P=0.03 Other sleep outcomes including total sleep time, number of nights with middle of the night awakenings, wake after sleep onset time, sleep quality indices, and sleep severity indices were no different between groups	Randomization methods not reported and there were differences in baseline sleep onset latency (78 vs. 51 min; p=0.03). High attrition (31%) and use of LOCF for missing data increases risk of bias. 17 patients (25%) discontinued due to AEs and 10 (15%) discontinued based on medical advice.
Morin, et al, 2020.[32] Sequential, multiple assignment, single-blind; RCT N=211	Step 1 (6 weeks) 1. Behavioral therapy (BT) 2. Zolpidem 5-10mg nightly Step 2 (for patients without remission) 1. Medication (zolpidem or trazodone 50-	Adults with chronic insomnia disorder	Response to therapy and remission after step 1 (at 6 weeks) and after step 2 (at 12 weeks) Response was defined based on reduction in the ISI of at least 8 points. Remission	<u>Step 1</u> Response to therapy 1. 45.5% 2. 49.7% OR 1.18; 95% CI 0.60-2.33 Remission 1. 38.03% 2. 30.3% OR 1.41; 95% CI 0.75-2.65 <u>Step 2 (n=108)</u> Change in proportion of patients with response 1. BT+zolpidem: 40.6% to 62.7%	High attrition rates (step 1: 15% vs. 25%; step 2: 25%) with higher attrition rates in patients initiating zolpidem treatment which may increase risk of bias. Response and remission rates were highest in patients randomized to initial BT followed by either zolpidem or CBT. In a subgroup of patients with a psychiatric comorbidity, response and remission rates were highest in

Setting: Canada and Colorado Duration: 12 months	150mg nightly) 2. Psychological therapy (BT or CBT) Patients who did not remit in step 1 were randomized to therapies in step 2		was defined as a total ISI score of less than 8.	OR 2.46; 95% CI 1.14-5.30 2. BT+CBT: 50.6% to 68.2% OR 2.09; 95% CI 1.01-4.35 3. Zolpidem+trazodone: 46.4% to 55.7%; P=NS 4. Zolpidem+BT: 52.9% to 47.9%; P = NS Change in proportion of patients with remission 1. BT+zolpidem: 38.1% to 55.9% OR 2.06; 95% CI 1.04-4.11 2. BT+CBT: 38.0% to 45.2%; P = NS 3. Zolpidem+trazodone: 31.4% to 49.4%; p=NS 4. Zolpidem+BT: 29.2% to 36.2%; P = NS	patients randomized to CBT or trazodone.

Abbreviations: AE = adverse events; BT = behavioral therapy; CBT = cognitive behavioral therapy; DB = double blind; ISI = insomnia severity index; LOCF = last observation carried forward; NS = non-significant; OR = odds ratio; PC = placebo controlled; RCT = randomized controlled trial; SD = standard deviation

NEW DRUG EVALUATION:

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Daridorexant 25 mg or 50 mg daily was FDA approved for treatment of insomnia in 2022 based on two phase 3, double-blind, placebo-controlled, RCTs. Trials were identically designed, though one study evaluated a lower dose of 10 mg. FDA approval was also supported by evidence from a phase 2 trial[4] and several small, short-term, RCTs evaluating safety of daridorexant in patients at least 65 years of age,[33] patients with obstructive sleep apnea,[34] patients with chronic obstructive pulmonary disease (COPD),[35] and patients with sedative drug use disorder.[36]

Overall, the phase 3 studies were well designed in order to minimize risk of bias (**Table 4**). However, both trials had extensive exclusion criteria which limit applicability to the general population. Patients who had psychiatric comorbidities, other sleep-wake disorders, alcohol or drug misuse, 15 or more apnea or hypopnea events per hour, or oxygen saturation less than 80% were excluded from the study.[3] As a method to control for and minimize the placebo effect, a patient-blinded placebo run-in period (13-24 days) was also required before randomization. Patients were required to meet baseline eligibility criteria for disturbed sleep and polysomnography during both screening and run-in periods. Treatment for insomnia has historically been associated with a very large placebo effect, and of the patients included in the run-in period, 50-54% of patients were excluded because they did not meet baseline inclusion criteria.[3] The primary reasons for exclusion were for apnea/hypopnea, oxygen saturation, or failure to meet subjective or objective baseline sleep disturbance criteria or polysomnography sleep parameters. Screening failure rate was slightly higher among patients identifying as Black compared to patients identifying as White which may result in a disproportionately larger population of White patients included in the study compared to the general population of patients who experience insomnia.[3] Other racial and ethnic subgroups were underrepresented in the studies.

Overall, only 25-28% of patients screened were included in these trials. Included patients were predominately female (64-69%) with an average age of 55-57 years, had been diagnosed with insomnia for approximately 10-11 years.[3] Additional required sleep parameters included an insomnia severity index of at least

15, wake after sleep onset (WASO) time of at least 30 minutes, latency to persistent sleep (LPS) of at least 20 minutes, and total sleep time (TST) of less than 7 hours.[3] Average values for the population are listed in **Table 4** are overall representative of a population with moderate to severe chronic insomnia.

Outcomes evaluated in these trials included both subjective and objective sleep parameters. Primary outcomes included WASO and LPS evaluated by polysomnography after 1 and 3 months of treatment. Magnitude of effect was generally comparable at 1 and 3 months for most outcomes. At 3 months, there was a least square mean difference from placebo in WASO time of 18 minutes with 50 mg nightly and 10-12 minutes with 25 mg nightly.[3] Compared to placebo, LPS improved by about 12 minutes with a 50 mg dose and 8-9 minutes with a 25 mg dose.[3] In Study 2, outcomes for 10 mg dose were not significantly improved compared to placebo.[3] While these results were statistically significant compared to placebo, it is unclear whether a mean improvement of less than 20 minutes in sleep maintenance time or less than 10 minutes in sleep latency would be clinically significant for most patients.

The two pre-specified secondary outcomes included total sleep time and change in the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleep domain score. The IDSIQ evaluates patient-reported impact of sleep on daytime symptoms and is divided into 3 domains of sleepiness, mood, and alert/cognition. The sleep domain is comprised of 4 items each rated 0-10 (max score of 40) with higher scores indicating more severe disease burden.[3] A within-person difference of 4 points was pre-specified as a clinically significant improvement on the sleep domain score.[3] In study 1, total sleep time improved by about 22 minutes at 1 month and 58 minutes at 3 months with a dose of 50 mg nightly compared to placebo.[3] For the 25 mg dose, the magnitude of benefit differed between the studies for self-reported total sleep time. Upon comparison of a 25 mg dose to placebo, self-reported total sleep time improved by 47.8 minutes (95% CI 41.3 to 54.3) in study 1 and 19.1 minutes (95% CI 10.1 to 28.0) in study 2 at 3 months.[3] With a 50 mg dose, IDSIQ sleep domain score was reduced (i.e., improved) by an average of -1.8 (95% CI -2.5 to -1.0) and -1.9 points (95% CI -2.9 to -0.9) compared to placebo at 1 and 3 months, respectively.[3] There was no difference in the IDSIQ sleep domain score with a 25mg dose compared to placebo in study 1, and study 2 found a statistically significant improvement of −1.3 points (95% CI −2.2 to −0.3) at 3 months compared to placebo.[3] Subgroup analyses for outcomes by age, sex, or center location demonstrated a similar direction of effect.[3]

There are currently no large trials comparing efficacy of daridorexant to other sleep medications. One small phase 2 trial for daridorexant did include an active comparison to zolpidem.[4] The primary goal of the trial was to evaluate dose response with daridorexant over a one month period, and statistical analyses compared to zolpidem were not performed. However, improvement in objective and subjective outcomes of WASO, LPS and total sleep time after 1 month had a similar magnitude of effect between zolpidem 10 mg and daridorexant 25-50 mg.[4]

These trials have limited applicability due to extensive exclusion criteria, and the magnitude of benefit and safety in patients with comorbid conditions is unknown. Due to stringent baseline insomnia criteria, the population studied is representative of those with moderate to severe insomnia, and the average time since the first insomnia diagnosis was over 10 years. The magnitude of benefit in patients with less severe disease is unknown. Despite use of a run-in period to minimize the placebo effect, patients randomized to placebo still had a significant improvement in sleep parameters. A long-term extension study evaluating maintenance of efficacy and long-term safety of daridorexant was recently completed but is not yet published.

Clinical Safety:

The safety profile of daridorexant is overall consistent with other orexin receptor antagonists used for the treatment of insomnia. Safety data was primarily derived from two phase 3 trials and a long-term extension study. The safety population included approximately 1232 patients who were exposed to 10-50 mg of daridorexant.[37] About 40% of these patients were older than 65 years of age and 46% were on therapy for more than 6 months.[37] Common adverse events associated with treatment included central nervous system (CNS) disorders such as headache (6-7% vs. 5% with placebo), somnolence/fatigue (5-6% vs. 4% with

placebo) and dizziness (2-3% vs. 2% with placebo).[37] Adverse events were slightly more common with higher doses. Nausea was also more common with daridorexant 50 mg compared to placebo (3% vs. 2%). Incidence of somnolence and fatigue increased with age, which may increase risk of falls in this population.[37]

Similar to other sedative drugs for insomnia, rare but serious adverse events are included in the labeling for daridorexant. These include parasomnias (e.g., sleep paralysis, hallucinations and narcolepsy/cataplexy-like symptoms), complex sleep behaviors (e.g., sleepwalking, sleep-driving, etc), worsening of depression and suicidal ideation, abuse/dependence, rebound insomnia, and respiratory depression.[37] Daridorexant is a central nervous system depressant and can cause impaired daytime functioning and wakefulness. Co-administration with other CNS depressants may have additive effects and patients with concomitant use of CNS depressants were excluded from clinical trials. Similarly, patients with underlying respiratory conditions resulting in sleep apnea, hypopnea or decreased oxygen saturation were excluded from clinical trials and risks of respiratory depression in these populations cannot be ruled out. Patients with comorbid psychiatric conditions were also excluded from clinical trials. Patients with psychiatric conditions, including insomnia, may be at increased risk of suicide, and there have been post-marketing reports of worsening depression, suicidal thoughts, and suicide attempts in patients treated with sedative hypnotics.[37] Daridorexant is undergoing evaluation by the DEA for controlled substance schedule and patients with history of substance use disorders were excluded from phase 3 trials. Close monitoring is recommended for patients with risk for substance abuse.[37] Physical dependence and withdrawal symptoms were not observed upon discontinuation of FDA-approved doses in phase 3 trials, but an abuse potential study documented similar "drug liking" ratings with use of daridorexant 100mg, zolpidem 30 mg and suvorexant 150mg.[37]

Because daridorexant is extensively metabolized by CYP enzymes, use is not recommended in conjunction with strong CYP3A4 inhibitors or inducers. A reduced dose (max 25 mg) is recommended if used in conjunction with moderate CYP3A4 inhibitors and in patients with moderate hepatic impairment.[37]

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Daytime function
2) Quality of life
3) Sleep onset and maintenance
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoints:

1) Wake time after sleep onset (WASO) at 1 and 3 months (sleep maintenance)
2) Latency to persistent sleep (LPS) at 1 and 3 months (sleep onset)

Table 3. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Orexin receptor antagonist which blocks binding of orexin A and orexin B to receptors in order to suppress wakefulness
Oral Bioavailability	62%; onset of 30 to 40 minutes
Distribution and Protein Binding	Volume of distribution = 31L 99.7% plasma protein binding
Elimination	57% feces, 28% urine (primarily as metabolites)
Half-Life	8 hours
Metabolism	89% via CYP3A4

Table 4. Comparative Evidence Table.

<table>
<tr><th>Ref./ Study Design</th><th>Drug Regimens/ Duration</th><th>Patient Population</th><th>N</th><th>Efficacy Endpoints</th><th>ARR/ NNT</th><th>Safety Outcomes</th><th>ARR/ NNH</th><th>Risk of Bias/ Applicability</th></tr>
<tr>
<td>1. Mignot, et al. 2022.[3]

MC, DB, PC, PG</td>
<td>1. daridorexant 50 mg every evening

2. daridorexant 25 mg every evening

3. placebo

Duration: 3 months randomized treatment period

- Screening period: 7-18 days
- Run-in period: 13-24 days
- Run-out period: 7 days
- Safety follow-up: 23 days

Patients could enroll in an optional extension period (9 months)</td>
<td><u>Demographics</u>:
- Female: 64-69%
- Mean age 55 years (SD 15)
- Age ≥65 years: 39%
- Race: White 88-93%
Black 6-10%
- Mean BMI: 26 kg/m^2
- Time since diagnosis:10-11 yrs
- WASO: 95-102 min
- LPS: 63-37 min
- Self-reported TST: 309-315 min
- Total sleep time: 318-328 min
- ISI: 19 (SD 4)
- IDSIQ sleep domain: 22 (SD 7)

<u>Key Inclusion Criteria</u>:
- Adults ≥ 18 years
- Insomnia diagnosis (DSM-5)
- Insomnia Severity Index ≥ 15
- Patient-reported history of disturbed sleep* for ≥3 months
- Patient-reported disturbed sleep* during baseline screening
- Baseline polysomnography: LPS ≥ 20 min, WASO ≥ 30 min, & mean total sleep time <7 hrs

<u>Key Exclusion Criteria</u>:
- Daytime napping ≥1 hr on ≥3 days per week
- History of suicidal ideation, suicide attempt, uncontrolled acute or chronic psychiatric conditions, severe depression
- Alcohol or drug misuse (including ≥ 1 pack per day of tobacco use)
- Apnea or hypopnea index of ≥15 events/hr or O_2 sat <80%</td>
<td><u>ITT</u>:
1. 310
2. 310
3. 310

<u>Attrition</u>:
1. 24 (8%)
2. 22 (7%)
3. 28 (9%)</td>
<td><u>Primary Endpoints</u>:
Change in WASO (min)
<table>
<tr><th></th><th>1 month</th><th>3 months</th></tr>
<tr><td>1</td><td>-29.0</td><td>−29.4</td></tr>
<tr><td>2</td><td>-18.4</td><td>−23.0</td></tr>
<tr><td>3</td><td>-6.2</td><td>−11.1</td></tr>
</table>
LSMD At 1 month
1 vs. 3: -22.8; 95% CI -28.0 to -17.6, p<0.0001
2 vs. 3: -12.2; 95% CI -17.4 to -7.0, p<0.0001
LSMD At 3 months
1 vs. 3: -18.3; 95% CI -23.9 to -12.7, p<0.0001
2 vs. 3: −11.9; 95% CI -17.5 to -6.2, p<0.0001

Change in LPS (min)
<table>
<tr><th></th><th>1 month</th><th>3 months</th></tr>
<tr><td>1</td><td>-31.2</td><td>-34.8</td></tr>
<tr><td>2</td><td>-28.2</td><td>-30.7</td></tr>
<tr><td>3</td><td>-19.9</td><td>-23.1</td></tr>
</table>
LSMD at 1 month
1 vs. 3: -11.4; 95% CI -16.0 to -6.7, p<0.0001
2 vs. 3: -8.3; 95% CI -13.0 to -3.6; p=0.0005
LSMD at 3 months
1 vs. 3: −11.7; 95% CI −16.3 to −7.0, p<0.0001
2 vs.3: -7.6; 95% CI -12.3 to -2.9, p<0.0001

<u>Secondary Endpoints</u>:
Change in Self-reported TST (min)
<table>
<tr><th></th><th>1 month</th><th>3 months</th></tr>
<tr><td>1</td><td>43.6</td><td>57.7</td></tr>
<tr><td>2</td><td>34.2</td><td>47.8</td></tr>
<tr><td>3</td><td>21.6</td><td>37.9</td></tr>
</table>
At 1 month
1 vs. 3: 22.1; 95% CI 14.4 to 29.7; p<0.0001
2 vs. 3: 12.6; 95% CI 5.0 to 20.3; p=0.0013
At 3 months
1 vs. 3: 57.7; 95% CI 51.2 to 64.2, p<0.0001
2 vs. 3: 47.8; 95% CI 41.3 to 54.3, p=0.033</td>
<td>NA for all</td>
<td><u>DC due to AE</u>:
1. 3 (1%)
2. 2 (1%)
3. 7 (2%)

<u>SAE</u>
1. 3 (1%)
2. 2 (1%)
3. 7 (2%)

<u>Accidental overdose</u>
1. 8 (3%)
2. 4 (1%)
3. 5 (2%)

<u>Fall</u>
1. 1 (<1%)
2. 1 (<1%)
3. 8 (3%)

<u>Sleep paralysis</u>
1. 1 (<1%)
2. 1 (<1%)
3. 0 (0%)

<u>Suicidal ideation or self-injury</u>
None</td>
<td>NA for all</td>
<td>Risk of Bias (low/high/unclear):
<u>Selection Bias</u>: Low. Randomized via interactive response technology system with allocation concealment. Baseline characteristics balanced.
<u>Performance Bias</u>: Low. Blinded with use of matching placebo for 3 month treatment period. Investigators not blinded for run-in period. Blinded safety board adjudicated AEs.
<u>Detection Bias</u>: Low. Investigators and patients blinded with use of matching placebo.
<u>Attrition Bias</u>: Low. ITT analysis used. About 9.4% missing data for all endpoints and treatment groups. Missing data was comparable between groups. Linear MMRM was used for each analysis and missing data was assumed to be comparable to other participants in the same treatment group. Sensitivity analysis evaluating various imputation methods resulted in comparable magnitude of effect.
<u>Reporting Bias</u>: Low. Outcomes reported as prespecified. Gatekeeping procedure used to adjust for multiplicity.
<u>Other Bias:</u> Unclear. Study sponsor was involved in study design, data collection, data analysis, data interpretation, & report writing.

Applicability:
<u>Patient</u>: About 28% of patients screened were included. Screening failure rate was slightly higher among Black individuals. Patients were most commonly excluded for apnea or hypopnea index ≥ 15 events/hr, O_2 Sat <80%, failure to meet subjective patient-reported sleep disturbance criteria, or failure to meet objective baseline polysomnography criteria. Due to stringent baseline insomnia criteria, population is representative of those with moderate to severe insomnia. Patients with comorbidities were excluded.
<u>Intervention</u>: Despite recommended use as a first-line treatment, few patients had prior CBT for insomnia. Dose range appropriate based on</td>
</tr>
</table>

		- Other sleep-wake disorders (restless leg syndrome, shift work. circadian rhythm disorder, rapid-eye-movement behavior disorder, narcolepsy) - Unstable medical condition, significant medical disorder or acute illness, ECG, or abnormal lab results within prior 1 month which could affect the patients safety or interfere with study assessments		**Change in IDSIQ - sleep domain score** 1: -3.8; -5.7 2: -2.8; -4.8 3: -2.0; -3.8 **At 1 month** 1 vs. 3: -1.8; 95% CI -2.5 to -1.0, p<0.0001 2 vs. 3: -0.8; 95% CI -1.5 to 0.01; p=0.055 (NS) **At 3 months** 1 vs. 3: -1.9; 95% CI -2.9 to -0.9; p=0.0002 2 vs. 3: -1.0; 95% CI -2.0 to 0.01; p=0.053 (NS)				phase 2 studies that demonstrated a dose response relationship for outcomes of WASO and LPS. Near maximal effect on sleep latency was observed at 10 mg but had no plateau effect on WASO when dosed up to 50 mg. Comparator: Placebo appropriate to determine efficacy. No active comparator, which could have informed place in therapy. Outcomes: Relatively large placebo effect, but both subjective and objective sleep measures had the same direction of effect. Setting: 75 sites in 10 countries from June 4, 2018 and Feb 25, 2020 (Australia, Canada, Denmark, Germany, Italy, Poland, Serbia, Spain, Switzerland, and the USA). US patients represented 31-34%.
2. Mignot, et al. 2022.[3] MC, DB, PC, PG	1. daridorexant 25 mg every evening 2. daridorexant 10 mg every evening 3. placebo Duration: see above	Demographics: - Female: 69% - Mean age 56-57 years (SD 14) - Age ≥65 years: 39% - Race: White 87-89% Black 5-9% - Mean BMI: 26 kg/m^2 - Time since diagnosis:10-12 yrs - WASO: 104-108 min - LPS: 67-72 min - Self-reported TST:307-308 min - Total sleep time: 307-316 min - ISI: 20 (SD 4) - IDSIQ sleep domain: 22 (SD 6) Key Inclusion Criteria: - See above Key Exclusion Criteria: - See above	ITT: 1. 309 2. 307 3. 308 Attrition: 1. 23 (7%) 2. 23 (7%) 3. 18 (6%)	Primary Endpoints: **Change in WASO (min)** 1: −24.2; -24.3 2: -15.3; -16.0 3: -12.6; -12.6 **LSMD At 1 month** 1 vs. 3: −11.6 (95% CI −17.6 to −5.6); p=0.0001 2 vs. 3: −2.7 (95% CI −8.7 to 3.2); p=0.37 (NS) **LSMD At 3 months** 1 vs. 3: -10.3 (95% CI -17.0 to −3.5); p=0.0028 2 vs. 3: −2.0 (95% CI −8.7 to 4.8); p=0.57 (NS) **Change in LPS (min)** 1: -26.5; -28.9 2: -22.6; -23.1 3: -20.0; -19.9 **LSMD at 1 month** 1 vs. 3: −6.5 (95% CI −12.3 to −0.6); p=0.030 2 vs. 3: −2.6 (95% CI −8.4 to 3.2); p=0.38 (NS) **LSMD at 3 months** 1 vs. 3: −9.0 (95% CI −15.3 to −2.7); p=0.0053 2 vs. 3: −3.2 (95% CI −9.5 to 3.1); p=0.32 (NS)	NA for all	DC due to AE: 1. 4 (1%) 2. 6 (2%) 3. 7 (2%) SAE: 1. 3 (1%) 2. 3 (1%) 3. 4 (1%) Accidental overdose 1. 4 (1%) 2. 4 (1%) 3. 1 (<1%) Fall 1. 3 (1%) 2. 4 (1%) 3. 3 (1%) Sleep paralysis 1. 2 (1%) 2. 0 (0%) 3. 0 (0%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low; see above. Placebo group had slightly more severe sleep variables (TST, WASO, LPS) at baseline compared to treatment groups but differences were small (difference of about 5 min TST, 2 min WASO; 4 min LPS). Performance Bias: Low; see above. Detection Bias: Low; see above. Attrition Bias: Low; see above. Reporting Bias: Low; see above. Other Bias: Unclear; see above. **Applicability**: Patient: About 25% of patients screened were included. See above. Intervention: See above. Comparator: See above. Outcomes: See above. Setting: 81 sites in 11 countries from May 29, 2018, and May 14, 2020 (Belgium, Bulgaria, Canada, Czech Republic, Finland, France, Germany, Hungary, South Korea, Sweden, and the USA). US patients represented 35-37%.

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Secondary Endpoints (at 3 months):
Change in Self-reported TST (min)
<table>
<tr><th></th><th>1 month</th><th>3 months</th></tr>
<tr><td>1</td><td>43.8</td><td>56.2</td></tr>
<tr><td>2</td><td>41.0</td><td>50.7</td></tr>
<tr><td>3</td><td>27.6</td><td>37.1</td></tr>
</table>
At 3 months
1 vs. 3: 19.1 (95% CI 10.1 to 28.0); p<0.0001
2 vs. 3: 13.6 (95 % CI 4.7 to 22.5); p =0.0028

Change in IDSIQ - sleep domain score
<table>
<tr><th></th><th>1 month</th><th>3 months</th></tr>
<tr><td>1</td><td>-3.5</td><td>-5.3</td></tr>
<tr><td>2</td><td>-3.2</td><td>-4.8</td></tr>
<tr><td>3</td><td>-2.8</td><td>-4.0</td></tr>
</table>
At 3 months
1 vs. 3: −1.3 (95% CI −2.2 to −0.3); p=0.012
2 vs. 3: −0.7 (95% CI −1.7 to 0.2); p=0.14 (NS)</td>
<td></td>
<td>Suicidal ideation or self-injury
1. 1 (<1%)
2. 1 (<1%)
3. 0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td colspan="8">Abbreviations: AE = adverse event; ARR = absolute risk reduction; BMI = body mass index; CBT = cognitive behavioral therapy; CI = confidence interval; DB = double-blind; DC = discontinuation; ECG = electrocardiogram; DC = discontinue; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition ; IDSIQ = Insomnia Daytime Symptoms and Impacts Questionnaire; ISI = insomnia severity index; ITT = intention to treat; LPS = latency to persistent sleep; LSMD = least squares mean difference; MC = multi-center; mITT = modified intention to treat; MMRM = mixed-effects model for repeated measures; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = non-significant; PC = placebo controlled; PG = parallel group ; PP = per protocol; SAE = severe adverse event; SD = standard deviation; TST = total sleep time; WASO = awake after sleep onset
* Disturbed sleep defined as all the following ≥ 30 min to fall asleep, ≥ 30 min awake during sleep time & total sleep time ≤ 6.5 hrs for ≥ 3 nights per week</td>
</tr>
</table>

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
melatonin	MELATONIN	TABLET	Y
zolpidem tartrate	AMBIEN	TABLET	Y
zolpidem tartrate	ZOLPIDEM TARTRATE	TABLET	Y
diphenhydramine HCl	NIGHTTIME SLEEP AID	CAPSULE	N
diphenhydramine HCl	SLEEP AID	CAPSULE	N
diphenhydramine HCl	SLEEP TIME	CAPSULE	N
diphenhydramine HCl	SLEEP AID	LIQUID	N
diphenhydramine HCl	SLEEP TIME	LIQUID	N
diphenhydramine HCl	NIGHTTIME SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP TABS	TABLET	N
doxepin HCl	DOXEPIN HCL	TABLET	N
doxepin HCl	SILENOR	TABLET	N
doxylamine succinate	SLEEP AID	TABLET	N
estazolam	ESTAZOLAM	TABLET	N
eszopiclone	ESZOPICLONE	TABLET	N
eszopiclone	LUNESTA	TABLET	N
flurazepam HCl	FLURAZEPAM HCL	CAPSULE	N
lemborexant	DAYVIGO	TABLET	N
midazolam HCl	MIDAZOLAM HCL	SYRUP	N
ramelteon	RAMELTEON	TABLET	N
ramelteon	ROZEREM	TABLET	N
suvorexant	BELSOMRA	TABLET	N
tasimelteon	HETLIOZ	CAPSULE	N
tasimelteon	HETLIOZ LQ	ORAL SUSP	N
temazepam	RESTORIL	CAPSULE	N
temazepam	TEMAZEPAM	CAPSULE	N
triazolam	HALCION	TABLET	N
triazolam	TRIAZOLAM	TABLET	N
zaleplon	ZALEPLON	CAPSULE	N
zolpidem tartrate	AMBIEN CR	TAB MPHASE	N
zolpidem tartrate	ZOLPIDEM TARTRATE ER	TAB MPHASE	N
zolpidem tartrate	EDLUAR	TAB SUBL	N
zolpidem tartrate	ZOLPIDEM TARTRATE	TAB SUBL	N
chloral hydrate	CHLORAL HYDRATE	SYRUP	
melatonin/pyridoxine HCl (B6)	MELATONIN-VITAMIN B6	TABLET	

Appendix 2: Abstracts of Comparative Clinical Trials

Castro LS, Otuyama LJ, Fumo-Dos-Santos C, Tufik S, Poyares D. Sublingual and oral zolpidem for insomnia disorder: a 3-month randomized trial. Revista brasileira de psiquiatria (Sao Paulo, Brazil : 1999). 2020;42(2):175-184.

OBJECTIVE: To evaluate the safety and efficacy of a 5 mg sublingual dose of zolpidem, compared to a 10 mg oral dose, at bedtime and "as needed" following middle-of-the-night awakenings.

METHODS: Participants were randomized into an oral group (oral zolpidem 10 mg and sublingual placebo at bedtime and "as-needed") and a sublingual group (oral placebo and sublingual zolpidem 5 mg at bedtime and "as-needed"). Participants underwent medical evaluation, polysomnography, the psychomotor vigilance test, and completed questionnaires.

RESULTS: Of 85 patients, 67 met the criteria for insomnia (48+/-10 years; 79% women) and were randomized. Of these, 46 completed 92+/-5 days of treatment. Mild-to-moderate adverse events were reported by 25% of the participants, including headache, sleepiness, and dizziness. Both treatments decreased middle-of-the-night awakenings by an average of -3.1+/-2.3 days/week and increased total sleep time by 1.5 hours. Changes in sleep quality and insomnia severity scores were also favorable and comparable between groups: variation depended on continuation of treatment. Regarding PSG findings, sleep latency decreased more in the sublingual group than the oral group (-14+/-42 vs. 10+/-29 min; p = 0.03). The psychomotor vigilance test showed minor residual effects 30 minutes after awakening, which reversed after 2 hours.

CONCLUSIONS: The safety and efficacy of both zolpidem formulations are comparable. The sublingual 5 mg dose induced sleep more rapidly., CLINICAL TRIAL REGISTRATION: NCT01896336.

Morin CM, Edinger JD, Beaulieu-Bonneau S, et al. Effectiveness of Sequential Psychological and Medication Therapies for Insomnia Disorder: A Randomized Clinical Trial. *JAMA Psychiatry.* 2020;77(11):1107-1115.

Importance: Despite evidence of efficacious psychological and pharmacologic therapies for insomnia, there is little information about what first-line treatment should be and how best to proceed when initial treatment fails., Objective: To evaluate the comparative efficacy of 4 treatment sequences involving psychological and medication therapies for insomnia and examine the moderating effect of psychiatric disorders on insomnia outcomes.

Design, Setting, and Participants: In a sequential multiple-assignment randomized trial, patients were assigned to first-stage therapy involving either behavioral therapy (BT; n = 104) or zolpidem (zolpidem; n = 107), and patients who did not remit received a second treatment involving either medication (zolpidem or trazodone) or psychological therapy (BT or cognitive therapy [CT]). The study took place at Institut Universitaire en Sante Mentale de Quebec, Universite Laval, Quebec City, Quebec, Canada, and at National Jewish Health, Denver, Colorado, and enrollment of patients took place from August 2012 through July 2017.

Main Outcomes and Measures: The primary end points were the treatment response and remission rates, defined by the Insomnia Severity Index total score.

Results: Patients included 211 adults (132 women; mean [SD] age, 45.6 [14.9] years) with a chronic insomnia disorder, including 74 patients with a comorbid anxiety or mood disorder. First-stage therapy with BT or zolpidem produced equivalent weighted percentages of responders (BT, 45.5%; zolpidem, 49.7%; OR, 1.18; 95% CI, 0.60-2.33) and remitters (BT, 38.03%; zolpidem, 30.3%; OR, 1.41; 95% CI, 0.75-2.65). Second-stage therapy produced significant increases in responders for the 2 conditions, starting with BT (BT to zolpidem, 40.6% to 62.7%; OR, 2.46; 95% CI, 1.14-5.30; BT to CT, 50.1% to 68.2%; OR, 2.09; 95% CI, 1.01-4.35) but no significant change following zolpidem treatment. Significant increase in percentage of remitters was observed in 2 of 4 therapy sequences (BT to zolpidem, 38.1% to 55.9%; OR, 2.06; 95% CI, 1.04-4.11; zolpidem to trazodone, 31.4% to 49.4%; OR, 2.13; 95% CI, 0.91-5.00). Although response/remission rates were lower among patients with psychiatric comorbidity, treatment sequences that involved BT followed by CT or zolpidem followed by trazodone yielded better outcomes for patients with comorbid insomnia. Response and remission rates were well sustained through the 12-month follow-up.

Conclusions and Relevance: Behavioral therapy and zolpidem medication produced equivalent response and remission rates. Adding a second treatment produced an added value for those whose insomnia failed to remit with initial therapies., Trial Registration: ClinicalTrials.gov Identifier: NCT01651442.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to March 14, 2022

Searches		Results	Type
1	exp Melatonin/		21698
2	exp Zolpidem/		1700
3	exp Diphenhydramine/		4475
4	exp Doxepin/		841
5	exp Doxylamine/		390
6	exp Estazolam/		111
7	exp Eszopiclone/		131
8	exp Flurazepam/		781
9	exp Orexin Receptor Antagonists/		467
10	lemborexant.mp.		64
11	exp Midazolam/		9374
12	ramelteon.mp.		458
13	suvorexant.mp.		316
14	tasimelteon.mp.		87
15	exp Temazepam/		674
16	exp Triazolam/		1239
17	zaleplon.mp.		430
18	exp Sleep Aids, Pharmaceutical/		8896
19	exp Benzodiazepines/		67755
20	daridorexant.mp.		27
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20		98736
22	exp "Sleep Initiation and Maintenance Disorders"/		15525
23	exp Sleep Wake Disorders/		100918
24	22 or 23		100918
25	21 and 24		4919
26	limit 25 to yr="2020 -Current"		352
27	limit 26 to (english language and humans)		312
28	limit 27 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial or "systematic review")		93

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use QUVIVIQ safely and effectively. See full prescribing information for QUVIVIQ.

QUVIVIQ (daridorexant) tablets, for oral use, [controlled substance schedule pending]
Initial U.S. Approval: [pending controlled substance scheduling]

----------INDICATIONS AND USAGE----------
QUVIVIQ is an orexin receptor antagonist indicated for the treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance. (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage is 25 mg to 50 mg once per night, taken orally within 30 minutes before going to bed, with at least 7 hours remaining prior to planned awakening. (2.1)
- Time to sleep onset may be delayed if taken with or soon after a meal. (2.1)
- Hepatic Impairment: (2.3)
  - Moderate hepatic impairment: Maximum recommended dosage is 25 mg no more than once per night.
  - Severe hepatic impairment: Not recommended.

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 25 mg, 50 mg. (3)

----------CONTRAINDICATIONS----------
QUVIVIQ is contraindicated in patients with narcolepsy. (4)

----------WARNINGS AND PRECAUTIONS----------
- CNS-Depressant Effects and Daytime Impairment: Impairs alertness and motor coordination including morning impairment. Risk increases when used with other central nervous system (CNS) depressants. For patients taking QUVIVIQ, caution against next-day driving and other activities requiring complete mental alertness. (5.1)
- Worsening of Depression/Suicidal Ideation: Worsening of depression or suicidal thinking may occur. (5.2)
- Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms: May occur with use of QUVIVIQ. (5.3)
- Complex Sleep Behaviors: Behaviors including sleepwalking, sleep-driving, and engaging in other activities while not fully awake may occur. Discontinue immediately if complex sleep behavior occurs. (5.4)
- Compromised Respiratory Function: Effect on respiratory function should be considered. (5.5, 8.7)
- Need to Evaluate for Co-morbid Diagnoses: Reevaluate if insomnia persists after 7 to 10 days. (5.6)

----------ADVERSE REACTIONS----------
The most common adverse reactions (reported in ≥ 5% of patients treated with QUVIVIQ and at an incidence ≥ than placebo) were headache and somnolence or fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Idorsia Pharmaceuticals Ltd at toll-free phone 1-833-400-9611 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong CYP3A4 inhibitors: Avoid concomitant use. (2.2, 7.1)
- Moderate CYP3A4 inhibitors: Maximum recommended dose is 25 mg. (2.2, 7.1)
- Moderate or Strong CYP3A4 inducers: Avoid concomitant use. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2022

Appendix 5: Key Inclusion Criteria

Population	Patients with insomnia
Intervention	Drugs in Appendix 1
Comparator	Drugs in Appendix 1 or placebo
Outcomes	Outcomes Sleep latency (SL) Total sleep time (TST) Wake after sleep onset (WASO) Quality of sleep (QOS) Sleep efficiency (SE) Number of awakenings (NOA)
Timing	At least 4 weeks
Setting	Outpatient

Appendix 6: Prior Authorization Criteria

Sedatives

Goals:

- Restrict use of sedatives to OHP-funded conditions. Treatment of uncomplicated insomnia is not funded; insomnia contributing to covered co-morbid conditions is funded.
- Prevent concomitant use of sedatives, including concomitant use with benzodiazepines or opioids.
- Limit daily zolpidem dose to the maximum recommended daily dose by the FDA.
- Permit use of melatonin in children and adolescents 18 years of age or younger.

Length of Authorization:

- Up to 12 months or lifetime (criteria-specific)

Requires PA:

- All sedatives (e.g., sedative hypnotics, hypnotics-melatonin agonists) except melatonin in children and adolescents. Melatonin is not covered for adults over 18 years of age.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Zolpidem Daily Quantity Limits

Generic	Brand	Max Daily Dose
Zolpidem	Ambien	10 mg
Zolpidem ER	Ambien CR	12.5 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for melatonin in an adult over 18 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #3
3. Is the request for zolpidem at a higher dose than listed in the quantity limit chart?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes:** Inform prescriber of preferred alternatives in class. Go to #5	**No:** Go to #5
5. Is the patient being treated under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for lifetime.	**No:** Go to #6
6. Has the patient been treated with a different non-benzodiazepine sedative, benzodiazepine, or opioid within the past 30 days?	**Yes:** Go to #7	**No:** Go to #9
7. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?	**Yes:** Go to #9 Document reason for switch and approve duplication for 30 days.	**No:** Go to #8

Approval Criteria		
8. Is concurrent sedative therapy part of a plan to switch and taper off a long-acting benzodiazepine (such as diazepam, clonazepam, or chlordiazepoxide) AND has the provider included a detailed strategy to taper? Note: a documented taper strategy should include planned dose reductions and length of time between each dose modification for at least the next few weeks. It should also include a documented follow-up plan to monitor progress and manage withdrawal symptoms (regular check-ins are essential for a successful taper). Triazolam may be discontinued without a taper in most cases (2-hour half-life prevents physical dependence).	**Yes:** Approve duplicate benzodiazepine therapy for the duration specified in the taper plan (not to exceed 6 months).	**No:** Pass to RPh. Deny; medical appropriateness.
9. Does the patient have a diagnosis of insomnia with obstructive sleep apnea?	**Yes:** Go to #10	**No:** Go to #11
10. Is patient on CPAP?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness. Sedative/hypnotics are contraindicated due to depressant effect.
11. Is the patient being treated for co-morbid: • Depression; • Anxiety or panic disorder; or • Bipolar disorder? **AND** Is there an existing claim history for treatment of the co-morbid condition (e.g., antidepressant, lithium, lamotrigine, antipsychotic, or other appropriate mental health drug)?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh; Go to #12

Approval Criteria		
12. RPh only: Is diagnosis being treated a funded condition and is there medical evidence of benefit for the prescribed sedative?	**Funded:** Document supporting literature and approve up to 6 months with subsequent approvals dependent on follow-up and documented response.	**Not Funded:** Go to #13
13. RPh only: Is this a request for continuation therapy for a patient with a history of chronic benzodiazepine use where discontinuation would be difficult or unadvisable?	**Yes:** Document length of treatment and last follow-up date. Approve for up to 12 months.	**No:** Deny; medical appropriateness

P&T/DUR Review: *6/22 (SS); 12/20 (AG); 7/18 (JP); 3/17; 11/20/14, 3/27/14, 5/18/06, 2/23/06, 11/10/05, 9/15/05, 2/24/04, 2/5/02, 9/7/01*
Implementation: *1/1/21; 8/15/18; 1/1/15, 7/1/14; 1/1/07, 7/1/06, 11/15/05*

Benzodiazepines

Goal(s):

Approve only for OHP-funded diagnoses.
Prevent inappropriate long-term benzodiazepine use beyond 4 weeks for new starts (no history within the last 120 days).
Approve long-term use only for indications supported by the medical literature.

Length of Authorization:

- 1 month to 12 months (criteria-specific)

Requires PA:

- All benzodiazepines used beyond 4 weeks. Short-term use does not require PA.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a malignant neoplasm or other end-of-life diagnosis (ICD10 C00.xx-D49.xx or Z51.5)?	**Yes:** Approve for 12 months	**No:** Go to #3
3. Is the diagnosis an OHP-funded diagnosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Does the patient have a seizure disorder diagnosis or is the patient enrolled in a program for short-term outpatient management of alcohol withdrawal syndrome? Note: benzodiazepines are not indicated for alcohol dependence.	**Yes:** Approve for 12 months for seizure disorder or up to 1 month for alcohol withdrawal	**No:** Go to #5
5. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber evaluated the PDMP at least once in the past 3 months for this patient?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #7

Approval Criteria		
7. Is the request for treatment of post-traumatic stress disorder (PTSD)? Note: Risks of benzodiazepine treatment outweigh benefits for patients with PTSD. Treatment with benzodiazepines is not recommended.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8
8. Is the request for treatment of anxiety or panic disorder?	**Yes:** Go to #9	**No:** Go to #10
9. Is the medication prescribed by or in consultation with a prescribing mental health specialist OR does the patient have a documented trial and failure, contraindication, intolerance, or inability to access recommended first-line treatment options including antidepressants AND psychotherapy (e.g. behavioral therapy, relaxation response training, mindfulness meditation training, eye movement desensitization and reprocessing)? Note: An adequate trial to determine efficacy of an SSRI or SNRI is 4-6 weeks.	**Yes:** Go to #12 Document trial, contraindication, or intolerance to treatment options.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend adequate trial of first-line therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
10. Is the request for treatment of psychosis, schizophrenia or schizoaffective disorder?	**Yes:** Go to #11	**No:** Go to #12

Approval Criteria		
11. Is the medication prescribed by or in consultation with a prescribing mental health specialist OR does the patient have an adequate trial and failure, contraindication, intolerance, or inability to access recommended first-line treatment options including second-generation antipsychotics AND psychotherapy (e.g. counseling, cognitive behavioral therapy, social skills training, or psychoeducation)? Note: For continued symptoms, assess adherence and dose optimization. For patients on an adequate dose of antipsychotic, guidelines recommend trial of a second antipsychotic or augmentation with a mood stabilizer.	**Yes:** Go to #12 Document trial, contraindication, or intolerance to treatment options.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend adequate trial of first-line therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
12. Is the patient on a concurrent sedative, hypnotic, muscle relaxant, or opioid?	**Yes:** Go to #13	**No:** Go to #14

Approval Criteria		
13. Is concurrent sedative therapy part of a plan to switch and taper off a long-acting benzodiazepine (such as diazepam, clonazepam, or chlordiazepoxide) AND has the provider included a detailed strategy to taper? Note: a documented taper strategy should include planned dose reductions and length of time between each dose modification for at least the next few weeks. It should also include a documented follow-up plan to monitor progress and manage withdrawal symptoms (regular check-ins are essential for a successful taper). Triazolam may be discontinued without a taper in most cases (2-hour half-life prevents physical dependence).	**Yes:** Approve duplicate benzodiazepine therapy for the duration specified in the taper plan (not to exceed 6 months).	**No:** Pass to RPh. Deny; medical appropriateness.
14. RPh only: Is there appropriate rationale to support long-term benzodiazepine use for this indication? For anxiety, panic disorder, or schizophrenia, provider rationale should include information from relevant chart notes. For other diagnoses, provider must document supporting medical literature.	**Yes:** Approve for up to 6 months.	**No:** Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for a decrease in daily dose OR a change in drug with the intent to taper the dose?	**Yes:** Approve for up to 6 months or length of taper, whichever is less.	**No:** Go to #2

Renewal Criteria		
2. Is the request for an increase in dose?	**Yes:** Go to #3	**No:** Go to #4
3. Has the patient failed all clinically appropriate first-line adjunct treatment options OR, when applicable, is the patient adherent to recommended first-line treatment options for their condition?	**Yes:** Go to #4	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of alternative therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
4. Is there documentation based on medical records that provider and patient have discussed whether benefits of long-term therapy (e.g. symptom improvement, social function, number of hospitalizations, etc) continue to outweigh risks of therapy (e.g. sedation, dependence, cognitive dysfunction and/or psychiatric instability)?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of gradual taper plan. Approval may be granted for up to 3 months to allow time to develop a taper plan. Subsequent requests must document progress toward taper.

P&T Review: *3/19 (SS); 9/18, 3/14*
Implementation: *5/1/19; 11/1/2018; 5/1/16*