

Lemborexant (Dayvigo™) New Drug Update

February 2020

Nonproprietary Name	lemborexant
Brand Name	Dayvigo
Manufacturer	Eisai
Form	Oral tablet
Strength	5 mg, 10 mg
FDA Approval	December 20, 2019
Market Availability	March 2020 (awaiting Drug Enforcement Agency [DEA] scheduling)
FDA Approval Classification	Standard Review
FDB Classification- Specific Therapeutic Class (HIC3)	To be determined

INDICATION¹

Lemborexant (Dayvigo) is an orexin receptor antagonist indicated for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Lemborexant will be a controlled substance. Scheduling remains pending by the DEA.

PHARMACOKINETICS

After administration of 2.5 mg to 75 mg doses of lemborexant, the maximum concentration (C_{max}) and area under the concentration curve (AUC) attained 24 hours post-dose increased slightly less relative to the dose. Lemborexant achieved time to maximum concentration (T_{max}) in approximately 1 to 3 hours and was delayed by 2 hours following a high-fat and high-calorie meal. The volume of distribution, protein binding, and blood to plasma concentration ratio are 1,970 L, 94%, and 0.65, respectively. Metabolism of lemborexant is primarily through cytochrome P450 (CYP) 3A4 and minimally through CYP3A5, with the major metabolite being M10. Excretion is mainly recovered in the feces versus the urine (57.4% versus 29.1%, respectively). The half-life is 17 hours for the 5 mg dose and 19 hours for the 10 mg dose.

CONTRAINDICATIONS/WARNINGS

Lemborexant is contraindicated in narcolepsy.

Lemborexant is a central nervous system (CNS) depressant that may impair the ability to perform daytime activities (e.g., driving) and have prolonged effects into the next day. Impairment is greater if taken with less than a full night of sleep or if taken above the recommended dose. Concomitant administration with other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants,

alcohol) may potentiate effects; therefore, dosage adjustments may be required. Concomitant administration with alcohol and other sedative hypnotics is not recommended. Lemborexant causes an increased risk of falls in the elderly.

Sleep paralysis, hypnagogic/hypnopompic hallucinations, or mild cataplexy may occur.

If complex sleep behaviors (e.g., sleep-walking, sleep-driving, engaging in other activities while not fully awake) occur, then lemborexant should be discontinued immediately.

The effects of lemborexant in patients with compromised respiratory function should be assessed. Lemborexant has not been studied in patients with severe obstructive sleep apnea (OSA) or severe chronic obstructive pulmonary disease (COPD).

Clinical studies demonstrated a higher incidence of suicidal ideation or behavior in lemborexant patients versus those on placebo, with an incidence ranging from 0.3% to 0.4% for lemborexant versus 0.2% for placebo. Worsening of depression and suicidal ideation in patients with depression may occur, which would require protective measures. These patients may purposely overdose; therefore, the smallest number of tablets should be administered at any one time.

Patients with insomnia should be evaluated for comorbid diagnoses. Failure to resolve after 7 to 10 days or worsening of insomnia may indicate a medical or psychiatric illness and may require further examination.

DRUG INTERACTIONS

- Concomitant use of lemborexant with strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin) or moderate CYP3A4 inhibitors (e.g., fluconazole, verapamil) should be avoided as AUC and C_{max} may increase, thereby potentiating adverse effects. A decreased dose is required when used concomitantly with weak CYP3A4 inhibitors (e.g., chlorzoxazone, ranitidine).
- Concomitant use of lemborexant with strong CYP3A4 inducers (e.g., rifampin, carbamazepine, St. John's wort) or moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil) should be avoided due to reduction of lemborexant efficacy.
- Alcohol should be avoided with lemborexant due to a possible increase of AUC and C_{max} , which may impair postural stability and memory.
- Concomitant administration of lemborexant with drugs that are CYP2B6 substrates (e.g., bupropion, methadone) may cause a decrease in the AUC of the CYP2B6 substrate. Patients should be monitored or the dose of the CYP2B6 substrate may need to be increased.

COMMON ADVERSE EFFECTS

The most common adverse effects (incidence \geq 5% and at a rate greater than that of placebo) reported with lemborexant relative to placebo, respectively, in clinical trials, were somnolence or fatigue (6.9% for 5 mg dose versus 9.6% for 10 mg dose versus 1.3% for placebo) and headache (5.9% for 5 mg dose versus 3.4% for placebo).

SPECIAL POPULATIONS

Pregnancy

Data for lemborexant in pregnancy are inadequate to advise of maternal or fetal risk.

Pregnant women exposed to lemborexant should be advised to register in the pregnancy exposure registry so that information can be collected and outcomes monitored during pregnancy.

Pediatrics

Safety and efficacy of lemborexant have not been established in pediatric patients (≤ 18 years of age).

Geriatrics

In clinical trials, no differences in pharmacokinetic profiles of lemborexant were reported between patients ≥ 65 years of age and younger populations. There is an increased risk of falls due to somnolence in doses higher than 5 mg in this population; caution should be exercised when used in the elderly.

Hepatic Impairment

Use of lemborexant is not recommended in patients with severe hepatic impairment. In patients with moderate hepatic impairment (Child-Pugh Class B), a decrease in dose is required. In patients with mild hepatic impairment (Child-Pugh Class A), the terminal half-life was not changed; however, patients may experience an increased risk of somnolence.

Renal Impairment

In severe renal impairment, the overall exposure was increased; therefore, there is an increased risk of somnolence. No dose adjustments are required for severe, moderate, or mild renal impairment.

DOSAGES

The recommended dosage is 5 to 10 mg once per night, immediately before bedtime, with ≥ 7 hours of sleep remaining before awakening. A delayed time to sleep onset may be seen if taken with or soon after a meal.

A maximum dose of 5 mg nightly is recommended in patients with moderate hepatic impairment or when used with concomitant weak CYP3A inhibitors.

CLINICAL TRIALS^{2,3,4,5}

A literature search was performed using “lemborexant” and “insomnia.”

In SUNRISE 1 (NCT02783729), a randomized, double-blind, parallel-group, placebo-controlled, active-comparator, phase 3 study, researchers evaluated 1,006 patients with insomnia (based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5] criteria) who reported sleep maintenance difficulties, with or without sleep onset difficulties. The study included females ≥ 55 years of age and males ≥ 65 years of age. Patients were randomized for 1 month to receive placebo, zolpidem tartrate extended-release (6.25 mg), or lemborexant (5 mg or 10 mg) nightly. The primary endpoint was the change from baseline in transformed latency to persistent sleep (LPS), as assessed by polysomnography, for lemborexant versus placebo. Secondary endpoints included changes from baseline in sleep efficiency (SEF) and wake after sleep onset (WASO; time to awakening after falling

asleep) versus placebo, as well as WASO in the second half of the night versus zolpidem. Lemborexant demonstrated statistical significance in sleep onset measured by LPS on nights 29 and 30 over placebo (lemborexant 5 mg treatment ratio, 0.77 [95% confidence interval {CI}, 0.67 to 0.89; $p < 0.001$]; lemborexant 10 mg treatment ratio, 0.72 [95% CI, 0.63 to 0.83; $p < 0.001$]). There was a statistically significant improvement in SEF over placebo (lemborexant 5 mg LSM treatment difference, 7.1% [95% CI, 5.6 to 8.5; $p < 0.001$]; lemborexant 10 mg LSM treatment difference, 8% [95% CI, 6.6 to 9.5; $p < 0.001$]). There was also a reduction in WASO versus placebo (lemborexant 5 mg WASO, -24 min [95% CI, -30 to -18; $p < 0.001$]; lemborexant 10 mg WASO, -25.4 min [95% CI, -31.4 to -19.3; $p < 0.001$]). In the second half of the night, WASO also improved in the lemborexant-treated group versus those treated with zolpidem (lemborexant 5 mg LSM treatment difference versus zolpidem, -6.7 min [95% CI, -11.2 to -2.2; $p = 0.004$]; lemborexant 10 mg LSM treatment difference versus zolpidem, -8 min [95% CI, 3.5 to 12.5; $p < 0.001$]).

SUNRISE 2 (NCT02952820), a phase 3, randomized, double-blind, placebo-controlled, multicenter, 6-month trial, assessed the efficacy of lemborexant in adult patients ≥ 18 years with a DSM-5 diagnosis of insomnia. Patients were randomized to placebo ($n=325$), lemborexant 5 mg ($n=323$), or lemborexant 10 mg ($n=323$) once daily at night and reported their outcomes in a sleep diary. The primary endpoint was the mean change from baseline to end of treatment at 6 months for patient-reported sleep onset latency (SOL), defined as the estimated number of minutes from the time patient attempted to sleep until onset of sleep. Secondary endpoints included change from baseline to end of treatment for patient-reported SEF and WASO. The median age was 55 years (range, 18 to 88 years), 68% were females, and 72%, 8%, and 17% were Caucasian, African American, and Japanese, respectively. Lemborexant demonstrated statistical superiority in the primary efficacy measure over placebo; it improved SOL versus placebo (lemborexant 5 mg SOL treatment effect ratio, 0.7 [95% CI, 0.6 to 0.8; $p < 0.05$]; lemborexant 10 mg SOL treatment effect ratio, 0.7 [95% CI, 0.6 to 0.8; $p < 0.05$]). For the secondary endpoints, lemborexant also showed statistically significant superiority over placebo (lemborexant 5 mg SEF treatment difference from placebo, 4.5% [95% CI, 2.2 to 6.9; $p < 0.05$]; lemborexant 10 mg SEF treatment difference from placebo, 4.7% [95% CI, 2.4 to 7; $p < 0.05$]). There was also a greater improvement in WASO versus placebo (lemborexant 5 mg WASO treatment difference from placebo, -17.5 min [95% CI, -27.3 to -7.6; $p < 0.05$]; lemborexant 10 mg WASO treatment difference from placebo, -12.7 min [95% CI, -22.4 to -3; $p < 0.05$]).

OTHER DRUGS USED FOR CONDITION^{6,7}

Other sedative hypnotics used to treat insomnia include select benzodiazepines, such as estazolam, flurazepam, quazepam, temazepam, and triazolam; barbiturates; a tricyclic antidepressant, doxepin (Silenor[®]); non-benzodiazepines, including eszopiclone (Lunesta[®]), zolpidem (Ambien[®]), and zaleplon; melatonin receptor agonists, such as ramelteon (Rozerem[®]); and another orexin receptor antagonist, suvorexant (Belsomra[®]).

PLACE IN THERAPY^{8,9,10}

Lemborexant (Dayvigo) blocks the neurotransmitter, orexin, in the hypothalamus which promotes wakefulness and is the second orexin receptor antagonist to be approved for the treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

The 2017 American Academy of Sleep Medicine (AASM) guidelines recommend psychological and cognitive behavioral therapy (CBT) in primary and secondary insomnia. Additionally, the AASM guidelines recommend that pharmacotherapy be used to treat patients who failed to respond to CBT (weak recommendation, low-quality evidence). The AASM recommends zaleplon, triazolam, and

ramelteon versus no treatment for sleep onset insomnia (weak recommendations), suvorexant and doxepin over no treatment for sleep maintenance insomnia (weak recommendations), and eszopiclone, zolpidem, and temazepam for both sleep onset and sleep maintenance insomnia (weak recommendations). Current AASM guidelines do not recommend one agent over another.

The 2016 American College of Physicians (ACP) practice guidelines recommend CBT as the initial treatment for chronic insomnia disorder (strong recommendation, moderate-quality evidence) and a risk versus benefit assessment be conducted by the clinician with the patient to decide whether to add pharmacological therapy if CBT alone was not successful (weak recommendation, low-quality evidence). In the general population, the ACP recommended eszopiclone and zolpidem (low to moderate quality evidence) for improved sleep outcomes such as SOL, total sleep time, and WASO. Ramelteon (low quality evidence) demonstrated no statistically significant difference for sleep outcomes in the same population. In the mixed general and adult populations, the ACP recommended suvorexant (moderate quality evidence) for improved treatment response and sleep outcomes. In older adults, eszopiclone was recommended (low quality evidence) for improved sleep outcomes and zolpidem and ramelteon (low quality evidence) for decreased SOL. Benzodiazepines were not addressed due to insufficient evidence of studies meeting the inclusion criteria.

The selection of a specific sedative hypnotic should be based on the need for initiation or maintenance of sleep, duration of action, comorbid conditions, contraindications, potential drug interactions, side effect profiles, abuse potential, and age. Furthermore, sedative hypnotics should be prescribed at the lowest dose that treats a patient's symptoms, and treatment should be individualized.

Lemborexant provides an additional treatment option for adult patients with insomnia characterized by sleep onset and/or sleep maintenance. Notably, in SUNRISE 1, lemborexant reduced wake after sleep onset in the second half of the night versus zolpidem; however, there is no clear clinical advantage over other sedative hypnotics for the management of insomnia. It will likely be a direct competitor to suvorexant as well as other effective medications for insomnia.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Sedative Hypnotics
Clinical Edit	<p>Initial Approval Criteria</p> <ul style="list-style-type: none"> ▪ Patient is ≥ 18 years old; AND ▪ Patient has a confirmed diagnosis of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance; AND ▪ Patient has tried nonpharmacological therapy and/or cognitive behavioral therapy (CBT); AND ▪ Patient does NOT have narcolepsy; AND ▪ Patient will NOT be on another sedative hypnotic; AND ▪ Patient does NOT have severe hepatic impairment; AND ▪ Patient is NOT taking any of the following drugs which should be avoided: <ul style="list-style-type: none"> – Strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin) or moderate CYP3A4 inhibitors (e.g., fluconazole, verapamil); OR – Strong CYP3A4 inducers (e.g., rifampin, carbamazepine, St. John’s wort) or moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil); AND ▪ Patient is prescribed no more than 5 mg lemborexant with weak CYP3A inhibitors (e.g., chlorzoxazone, ranitidine) and in patients with moderate hepatic impairment; AND ▪ Prescriber attestation that underlying physical conditions (e.g., pain, discomfort, environmental issues) and/or comorbid conditions have been evaluated and treated, yet symptoms of insomnia persist; AND ▪ Prescriber attestation that there are no concurrent medications (e.g., stimulants, selective serotonin reuptake inhibitors [SSRIs], decongestants, steroids) that may cause insomnia. <p>Renewal Criteria</p> <ul style="list-style-type: none"> ▪ Patient must continue to meet the initial criteria above; AND ▪ Prescriber attestation of efficacy; AND ▪ Patient has NOT experienced treatment-limiting adverse effects (e.g., worsening of depression, suicidal ideation, falls due to somnolence, complex sleep behaviors such as sleep-walking, sleep-driving, and engaging in other activities while not fully awake).
Quantity Limit	30 tablets/30 days
Duration of Approval	Initial: 6 months Renewal: 6 months
Drug to Disease Hard Edit	Narcolepsy

REFERENCES

- 1 Dayvigo [package insert]. Woodcliff Lake, NJ; Eisai; December 2019.
- 2 Rosenberg R, Murphy P, Zammit G, et al. Comparison of lemborexant with placebo and zolpidem tartrate extended release for the treatment of older adults with insomnia disorder. *JAMA Netw Open*. 2019; 2: e1918254. DOI: 10.1001/jamanetworkopen.2019.18254. Available at: <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2758000>. Accessed February 6, 2020.
- 3 Dayvigo [package insert]. Woodcliff Lake, NJ; Eisai; December 2019.
- 4 Study of the efficacy and safety of lemborexant in subjects 55 years and older with insomnia disorder (SUNRISE 1). Identifier: NCT02783729. Available at: <https://clinicaltrials.gov/ct2/show/results/NCT02783729?term=sunrise+1&draw=2&rank=1>. Accessed February 6, 2020.
- 5 Long-term study of lemborexant in insomnia disorder (SUNRISE 2). Identifier: NCT02952820. Available at: <https://clinicaltrials.gov/ct2/show/NCT02952820?term=sunrise+2&draw=2&rank=1>. Accessed February 6, 2020.
- 6 Pharmacological treatment of insomnia. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4634348/>. Accessed February 6, 2020.
- 7 Clinical Pharmacology. Available at: www.clinicalpharmacology.com. Accessed February 6, 2020.
- 8 Sateia MJ, Buysse D, Krystal AD, et al. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2017; 13(2):307-342. Available at: <http://www.aasmnet.org/practiceparameters.aspx?cid=109>. Accessed February 6, 2020.
- 9 Qaseem A, Kansagara D, Forcica MA, et al. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians 2016. *Ann Intern Med*. 2016; 165(2):125-133. Available at: <https://annals.org/aim/fullarticle/2518955/management-chronic-insomnia-disorder-adults-clinical-practice-guideline-from-american>. Accessed February 11, 2020.
- 10 Behavioral and pharmacologic therapies for chronic insomnia in adults. Available at: <https://www.uptodate.com/contents/behavioral-and-pharmacologic-therapies-for-chronic-insomnia-in-adults#H3553718232>. Accessed February 12, 2020.