Lemborexant (Dayvigo®)
FDA approved December 2019 (Eisai Inc); Schedule IV controlled substance

Indications: Insomnia characterized by difficulties with sleep onset and/or maintenance

Mechanism of action

- Blocks the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R, presumed to suppress wake drive

Dosage	5 mg qhs taken immediately before going to bed, with at least 7 hours remaining before planned time of awakening. Max dose 10 mg
Hepatic impairment	Moderate: 5 mg no more than once per night Severe: Not recommended (not studied)
Administration	- Administer without food prior to bedtime, at same time every night - Onset of action delayed with food, do not administer with (or soon after a meal)
How Supplied	5 & 10 mg tabs

Adverse Reactions

Most frequently reported AEs (≥5% & at least twice of placebo): Somnolence

Table 1: Adverse Reactions Reported in ≥2% of DAYVIGO-Treated Patients and at a Greater Frequency than Placebo-Treated Patients During the First 30 Days of Study 1 and Study 2

	Placebo n=528 (%)	DAYVIGO 5 mg n=580 (%)	DAYVIGO 10 mg n=582 (%)
Somnolence or fatigue*	1.3	6.9	9.6
Headache	3.4	5.9	4.5
Nightmare or abnormal dreams	0.9	0.9	2.2

*Combines preferred terms somnolence, lethargy, fatigue, sluggishness

Warnings and Precautions

CNS Depressant Effects & Daytime Impairment	Risk increases with dose or if used with other CNS depressants (eg, benzos, opioids, TCAs, alcohol). Use with other drugs to treat insomnia is not recommended
Sleep Paralysis, Hypnogogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms	Risk of sleep paralysis (inability to move or speak for up to several minutes during sleep-wake transitions), hypnagogic/hypnopompic hallucinations, and mild cataplexy-like symptoms can occur with lemborexant. Cataplexy symptoms may include leg weakness lasting from seconds to a few minutes
Complex Sleep Behaviors	Sleep related activities such as “sleep driving” & other behaviors (eg, preparing and eating food, making phone calls, or having sex), with amnesia for the event, have been reported
Compromised Respiratory Function	Use with caution in patients with respiratory compromise, COPD, or sleep apnea
Worsening of Depression/Suicidal Ideation	Use with caution in patients with depression. The incidence of suicidal ideation or suicidal behavior was higher in patients receiving lemborexant than in those receiving placebo. Consider prescribing the lowest number of tablets to avoid intentional overdose

Need to Evaluate for Co-morbid Diagnoses	Reevaluate if insomnia persists after 7 to 10 days of treatment

Contraindication: Narcolepsy

Interactions

Concomitant Medication	Effect
Strong or moderate CYP3A inhibitors Strong CYP3A inhibitors: itraconazole, clarithromycin Moderate CYP3A inhibitors: fluconazole, verapamil	Avoid concomitant use (increased r/o AEs)
Weak CYP3A inhibitors Examples: chlorzoxazone, ranitidine	Max recommended dose 5 mg
Strong and Moderate CYP3A Inducers Strong CYP3A inducers: rifampin, carbamazepine, St. John's wort. Moderate CYP3A inducers: bosentan, efavirenz, etravirine, modafinil	Avoid concomitant use (may reduce efficacy)
Alcohol	Concomitant use increases lemborexant C_{max} & AUC. Avoid alcohol use with lemborexant

Pharmacokinetics

Effect of food	High-fat & high-calorie meal delay T_{max} & reduce C_{max}
T_{max}	1 to 3 hours
Half-life	17 hours (5 mg) and 19 hours (10 mg)
Metabolism	primarily metabolized by CYP3A4
Excretion	Urine (29%); feces (57%)

Clinical Efficacy

- The efficacy of Dayvigo was evaluated in two clinical studies in patients who met DSM-5 criteria for insomnia disorder.
- Study 1 was a 6-month, randomized, double-blind, placebo-controlled, multi-center study in 971 patients 18 years of age or older. The primary endpoint was the mean change from baseline for log-transformed subjective sleep onset latency (sSOL), defined as the estimated minutes from the time that the patient attempted to sleep until sleep onset.
    - Dayvigo 5 mg and 10 mg demonstrated statistically significant superiority based on sSOL compared to placebo ($p < 0.05$).
- Study 2 was a 1-month, randomized, double-blind, placebo- and active-controlled, multi-center, parallel-group study in 1,006 female patients 55 years of age and older and male patients 65 years of age and older. The primary endpoint was the mean change in log-transformed latency to persistent sleep (LPS) from baseline, as measured by overnight polysomnography (PSG) monitoring. LPS was defined as the number of minutes from lights off to the first 10 consecutive minutes of non-wakefulness.
    - Dayvigo 5 mg and 10 mg demonstrated statistically significant superiority based on LPS compared to placebo ($p < 0.05$).
- Study considerations:
    - The primary endpoint of sSOL is patient-reported measure. As a widely-used measurement of sleep assessment, subjective reporting data is a useful surrogate measure for perception of sleep quality.

- The primary endpoint of LPS is an objective measure based on results from lab data. Polysomnographic data is best for capturing the physiologic response to therapy, but does represent patient's perceived response or improvements to daytime functioning or quality of life. Its usefulness as a marker for subjective outcomes and clinically relevant outcomes is unknown.
- There is no evidence that therapy with Dayvigo leads to improvements in clinically meaningful endpoints, such as work productivity and daytime function

Comments/Role in Therapy

- Lemborexant, the 2nd orexin receptor antagonist, is expected to less likely cause cognitive impairment / confusion the following day (thought to suppress wake drive rather than promoting sleepiness)
  - drowsiness - the most commonly reported side effect
  - can impair driving and other activities that require alertness. For clients on lemborexant 10 mg, caution against driving & other activities requiring complete mental alertness
  - safety data over a 12-month period
  - sleep onset and sleep maintenance efficacy data over a six-month treatment period
- Studies suggest that lemborexant lead to improved sleep onset and sleep maintenance even into the second half of the night
- Lemborexant vs Suvorexant (the 1st FDA approved orexin receptor antagonist):
  - Without head-to-head trials, comparison between lemborexant and suvorexant is speculative
  - The safety profile of lemborexant and suvorexant appears to be generally similar
  - Lemborexant has longer half life
    - Suvorexant: ~12 hours
    - Lemborexant 17 hours (5 mg), 19 hours (10 mg)
  - Findings of a randomized double-blind study to determine the abuse potential of single oral doses of lemborexant compared to zolpidem, suvorexant and placebo in healthy, non-dependent, recreational sedative users concluded that the abuse potential of lemborexant may be similar to zolpidem but larger than suvorexant
  - Of note, a 2020 study that is currently in press (Kishi, Taro, et al.) conducted a meta-analysis comparing the results of the two medications. They found that lembrorexant has higher efficacy, but the full text post-peer review is not yet available. Based on this information, it is likely that lembrorexant is comparable or superior to suvorexant
    - Lemborexant was superior to placebo in all efficacy outcomes.
    - Lemborexant might have some benefits for insomnia compared with suvorexant.
    - Lemborexant 10 mg/d had a risk of somnolence
- RCT compared lemborexant (5mg or 10mg), zolpidem ER (6.25mg) and placebo
  - Participants were 55 years and older with insomnia disorder characterized by reported sleep maintenance difficulties and confirmed by sleep history, sleep diary, and polysomnography. Participants could have also had sleep onset difficulties.
  - Lemborexant therapy significantly improved both sleep onset and sleep maintenance, including in the second half of the night, compared with both placebo and zolpidem measured objectively using polysomnography
  - Lemborexant therapy was generally well tolerated

        - Fall was reported as a treatment-emergent AEs by 4 participants, all of whom received lemborexant 5 mg, but none were considered related to the study drug by the investigator
        - Sleep paralysis was reported by 1 participant receiving lemborexant 5 mg and 3 participants receiving lemborexant 10 mg therapies. Considered by invesigator to be mild severity
        - No AEs were adjudicated as cataplexy & no complex sleep-related behaviors were reported
        - No evidence of suicidality was found, and no notable findings were reported for clinical laboratory tests, vital signs, weight, or electrocardiograms
    - Study Limitations
        - The study was restricted to participants 55 years and older; therefore, a fixed, albeit age-appropriate and sex-appropriate, dose of zolpidem was used
        - Long-term effects of lemborexant therapy are not yet known given short term study period of 1 month
- Eisai is exploring a phase 3 trial for irregular sleep-wake rhythm disorder in Alzheimer's patients after a phase 2 study demonstrated that lemborexant could be effective in pts with Alzheimers

Therapeutic category

FDA-Approved Guideline-Recommended First-Line Products for Insomnia and Comparative Cost [5]

Brand (generic)	Dosage Form(s) & Strength(s)	Dosing Regimen	Cost per 30 Days (AWP)[a]	Formulary Status (BHRS vs CMC vs HPSM MC)		
Orexin Receptor Agonists						
Dayvigo (lemborexant)	Oral tablets: 5 mg, 10 mg	• 5 mg tablet by mouth (PO) once per night taken within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening • If the 5 mg dose is well-tolerated but not effective, the dose can be increased, not to exceed 10 mg once daily	**Brand only:** $274.80 (all strengths flat-priced)	NF	NF	NF
Belsomra (suvorexant)	Oral tablets: 5 mg, 10 mg, 15 mg, 20 mg	• 10 mg tablet PO once per night taken within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening • If the 10 mg dose is well-tolerated but not effective, the dose can be increased, not to exceed 20 mg once daily	**Brand only:** $365.70 (all strengths flat-priced)	PA	T2 QL	T2 QL
Benzodiazepine Receptor Agonists (BzRAs)						
Lunesta (eszopiclone)	Oral tablets: 1 mg, 2 mg, 3 mg	• 1 mg tablet PO once per night taken immediately before bedtime, with at least 7-8 hours remaining before the planned time of awakening • If the 1 mg dose is well-tolerated but not effective, the dose can be increased, not to exceed 3 mg once daily	**Brand:** $564.48 **Generic:** $7.58	T1 QL	T1 QL	T1 QL

Brand (generic)	Dosage Form(s) & Strength(s)	Dosing Regimen	Cost per 30 Days (AWP)[a]	Formulary Status (BHRS vs CMC vs HPSM MC)		
Sonata (zaleplon)	Oral capsules: 5 mg, 10 mg	• 10 mg capsule PO once per night taken immediately before bedtime or after the patient has gone to bed and has experienced difficulty falling asleep • If the 10 mg dose is well-tolerated but not effective, the dose can be increased, not to exceed 20 mg once daily	**Generic only:** $9.00 to $9.45	T1 QL	T1 QL	T1 QL
Ambien (zolpidem)	Oral tablets: 5 mg, 10 mg	• 5 mg (women) and 5 or 10 mg (men) tablet PO once per night taken immediately before bedtime, with at least 7-8 hours remaining before the planned time of awakening • If the 5 mg dose is well-tolerated but not effective, the dose can be increased, not to exceed 10 mg once daily	**Brand:** $635.10 **Generic:** $2.70	T1 QL	T1 QL	T1 QL
Ambien CR (zolpidem ER)	Oral extended-release tablets: 6.25 mg, 12.5 mg	• 6.25 mg (women) and 6.25 or 12.5 mg (men) tablet PO once per night taken immediately before bedtime, with at least 7-8 hours remaining before the planned time of awakening • If the 6.25 mg dose is well-tolerated but not effective, the dose can be increased, not to exceed 12.5 mg once daily	**Brand:** $635.10 **Generic:** $22.50	NF	NF	NF
Intermezzo (zolpidem SL)	Oral sublingual (SL) tablets: 1.75 mg, 3.5 mg	• 1.75 mg (women) and 3.5 mg (men) SL tablet PO under the tongue taken only once per night if needed • Take only if 4 hours of bedtime remain before the planned time of waking	**Brand:** $446.76 **Generic:** $237.05	NF	NF	NF
Edluar (zolpidem SL)	Oral SL tablets: 5 mg, 10 mg	• 5 mg (women) and 5 or 10 mg (men) SL tablet PO once per night taken immediately before bedtime • If the 5 mg dose is well-tolerated but not effective, the dose can be increased, not to exceed 10 mg once daily	**Brand only:** $448.86	NF	NF	NF
Zolpimist (zolpidem)	Oral spray: 5 mg (4.5 mL, 7.7 mL)	• 5 mg (women) and 5 or 10 mg (men) oral spray per night taken immediately before bedtime, with at least 7-8 hours remaining before the planned time of awakening • If the 5 mg dose is well-tolerated but not effective, the dose can be increased, not to exceed 10 mg once daily	**Brand only:** $395.40 to $790.80	NF	NF	NF
Benzodiazepine (BZD)						

Brand (generic)	Dosage Form(s) & Strength(s)	Dosing Regimen	Cost per 30 Days (AWP)[a]	Formulary Status (BHRS vs CMC vs HPSM MC)		
Restoril (temazepam)	Oral capsules: 7.5 mg, 15 mg, 22.5 mg, 30 mg	• 15 mg capsule PO given 30 minutes before bedtime. If needed, may increase to 30 mg PO before bedtime. • In debilitated patients, initiate with 7.5 mg PO at bedtime, and generally, do not exceed 15 mg PO at bedtime. • In some patients, 7.5 mg/night may be sufficient.	**Brand:** $1,062.11 to $1,188.18 **Generic:** $2.08 to $165.18	T1 QL	T1 QL	T1 QL
Melatonin Receptor Agonist						
Rozerem (ramelteon)	Oral tablet: 8 mg	• 8 mg tablet PO within 30 minutes of going to bed • Total daily dose should not exceed 8 mg	**Brand:** $466.83 **Generic:** $104.92	T1 QL	T1 QL	T1 QL

[a] Estimated cost per 30 days based on unit AWP for brands and WAC for generics per Medispan as of 12/31/2019.

Formulary Considerations:

Add to BHRS formulary with PA requirement
PA criteria same as Belsomra:

- FDA approved indication
- Documentation that patient has tried and failed three formulary agents (noncontrolled)
- Quantity limit #30/30DS

References:

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