PDL DRUG REVIEW

Proprietary Name: Dayvigo®
Common Name: lemborexant
PDL Category: Sedative Hypnotics

Comparable Products	Preferred Drug List Status
Zolpidem	Preferred

Summary

Pharmacology/Usage: Lemborexant, the active ingredient of Dayvigo®, is an orexin receptor antagonist. Its mechanism of action is presumed to be through antagonism of orexin receptors. The orexin neuropeptide signaling system plays a role in wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress wake drive.

Dayvigo® is a Schedule IV controlled substance. As individuals with a history of abuse or addiction to alcohol or other drugs may be at increased risk for abuse and addiction to Dayvigo®, follow such patients carefully.

Indication: For the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women to assess for drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Dayvigo® during pregnancy. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 5mg, 10mg

Recommended Dosage: Take no more than 5 mg once per night, immediately before going to bed, with at least 7 hours remaining before the planned time of awakening. The dose may be increased to the maximum recommended dose of 10mg based on clinical response and tolerability. Time to sleep onset may be delayed if taken with or soon after a meal.

Dose adjustments are not required with mild, moderate, or severe renal impairment; however, exposure was increased in patients with severe renal impairment. Patients with severe renal impairment may experience an increased risk of somnolence. Use has not been studied in patients with severe hepatic impairment; thus, use in this population is not recommended. Patients with mild hepatic impairment may experience an increased risk of somnolence. Dose adjustments are recommended in patients with moderate hepatic impairment (maximum of 5mg no more than QHS).

Drug Interactions: Avoid concomitant use of Dayvigo® with strong or moderate CYP3A inhibitors. The maximum recommended dose of Dayvigo® with weak CYP3A inhibitors is 5mg no more than once per night. Avoid the concomitant use of Dayvigo® with strong or moderate CYP3A inducers.

Patients receiving Dayvigo® and CYP2B6 substrates (e.g. methadone, bupropion) concurrently should be monitored for adequate clinical response. Increasing the doses of CYP2B6 substrates may be considered as needed.

Avoid alcohol consumption with Dayvigo®.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Dayvigo® 5mg/10mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included somnolence or fatigue (5.6%/8.3%), headache (2.5%/1.1%), and nightmare or abnormal dreams (0%/1.3%). Others included sleep paralysis (1.3%/1.6%) and hypnagogic hallucinations (0.1%/0.7%).

Dayvigo® is a CNS depressant that can impair daytime wakefulness even when used as prescribed. Driving ability was impaired in some subjects taking Dayvigo® 10mg. The risk of daytime impairment is increased if Dayvigo® is taken with less than a full night of sleep remaining or if a higher than recommended dose is taken. If Dayvigo® is taken in these circumstances, patients should be cautioned against driving and other activities that require complete mental alertness. Co-administration with other CNS depressants (e.g. benzodiazepines, opioids, TCAs, alcohol) increases the risk of CNS depression, which can cause daytime impairment. Dose adjustments of Dayvigo® and other concomitant CNS depressants may be necessary when administered together due to potentially additive effects. The use of Dayvigo® with other drugs to treat insomnia is not recommended.

Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, and hypnagogic hallucinations can occur with Dayvigo® use. Symptoms similar to mild cataplexy can occur with Dayvigo®.

Complex sleep behaviors have been reported to occur with the use of hypnotics, such as Dayvigo®. Complex sleep behaviors may occur following the first or any subsequent use of Dayvigo®, with or without the concomitant use of alcohol and other CNS depressants. Discontinue Dayvigo® immediately if a patient experiences a complex sleep behavior.

The effect of Dayvigo® on respiratory function should be considered if prescribed to patients with compromised respiratory function. Dayvigo® has not been studied in patients with moderate to severe obstructive sleep apnea (OSA) or in patients with chronic obstructive pulmonary disease (COPD).

In clinical studies, the incidence of suicidal ideation or any suicidal behavior was higher in patients receiving Dayvigo® than placebo (0.3% for 10mg, 0.4% for 5mg, and 0.2% for placebo). In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions have been reported. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdose is more common in this group of patients; thus, the fewest number of tablets that is feasible should be prescribed at any one time. The emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Contraindications: In patients with narcolepsy

Manufacturer: Eisai Inc

Analysis: The efficacy of Dayvigo® was assessed in 2 clinical trials that included patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance. Study 1 was a 6-month, multicenter, randomized, double-blind, placebo-controlled study that included adults (≥18 years of age) who met DSM-5

criteria for insomnia disorder (N=971). The included patients had a median age of 55 years, while 68% were female and 72% were white.

The primary endpoint of study 1 was the mean change from baseline to the end of treatment for log-transformed patient-reported (subjective) sleep onset latency (sSOL), defined as the estimated minutes from the time that the patient attempted to sleep until sleep onset. Pre-specified secondary endpoints for sleep maintenance were change from baseline to end of treatment for patient-reported sleep efficiency (sSEF) and wake after sleep onset (sWASO). sSEF is defined as the proportion of time spent asleep per time in bed. sWASO is defined as the minutes of wake from the onset of sleep until wake time.

Results suggested that Dayvigo® 5mg and 10mg demonstrated statistically significant superiority on the primary efficacy measures as compared with placebo, as well as the secondary endpoints of sSEF and sWASO. Results can be seen in the table below, which was adapted from the prescribing information.

Endpoint	Treatment	N	Baseline mean	Month 6 least square mean	Treatment effect
Sleep onset, sSOL (minutes)	Dayvigo® 5mg*	316	43.0	20.0	0.7
	Dayvigo® 10mg*	315	45.0	19.2	0.7
	placebo	318	45.0	27.3	(ratio vs placebo)[1]
Sleep maintenance, sSEF (%)	Dayvigo® 5mg*	316	63.1	75.9	4.5
	Dayvigo® 10mg*	315	62.0	75.9	4.7
	placebo	318	61.3	71.4	(%)[2]
Sleep maintenance sWASO (minutes)	Dayvigo® 5mg*	316	132.8	87.9	-17.5
	Dayvigo® 10mg*	315	136.8	92.7	-12.7
	placebo	318	132.5	105.3	(minutes)[2]

*statistically significantly superior to placebo after adjustment ($p<0.05$).

[1] Treatment effect refers to the ratio, such that a smaller ratio corresponds to a greater improvement

[2] Treatment effect refers to the treatment difference, such that a larger value for sSEF and smaller value for sWASO correspond to greater improvement

Study 2 was a 1-month, multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group study that included adult female (≥55 years) and male (≥65 years) patients who met DSM-5 criteria for insomnia disorders. Included patients had a median age of 63 years, while 86% were female and 72% were white. Patients were randomized to placebo, Dayvigo® 5mg or 10mg, or active comparator once nightly. Information was not found in the prescribing information for the active comparator.

The primary outcome was the mean change in log-transformed latency to persistent sleep (LPS) from baseline to end of treatment (days 29/30), 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. The pre-specified secondary efficacy endpoints were the mean change from baseline to end of treatment (days 29/30) in sleep efficiency (SEF) and wake after sleep onset (WASO) measured by PSG.

Results suggested that Dayvigo® 5mg and 10mg demonstrated statistically significant superiority on the primary efficacy measure, LPS, compared to placebo. In addition, Dayvigo® 5mg and 10mg demonstrated statistically

significant improvement in SEF and WASO compared to placebo. Results can be seen in the table below, which was adapted from the prescribing information.

Endpoint	Treatment	N	Baseline mean	Day 29/30 least square mean	Treatment effect
Sleep onset, LPS (minutes)	Dayvigo® 5mg*	266	33.0	15.5	0.8
	Dayvigo® 10mg*	269	33.3	14.5	0.7
	placebo	208	33.6	20.0	(ratio vs placebo)[1]
Sleep maintenance, SEF (%)	Dayvigo® 5mg*	266	68.4	80.7	7.1
	Dayvigo® 10mg*	269	67.8	82.7	8.0
	placebo	208	68.9	74.6	(%)[2]
Sleep maintenance WASO (minutes)	Dayvigo® 5mg*	266	113.4	68.3	-24.0
	Dayvigo® 10mg*	269	114.8	66.9	-25.3
	placebo	208	111.7	92.2	(minutes)[2]

*statistically significantly superior to placebo after adjustment ($p<0.05$).

[1] Treatment effect refers to the ratio, such that a smaller ratio corresponds to a greater improvement

[2] Treatment effect refers to the treatment difference, such that a larger value for SEF and smaller value for WASO correspond to greater improvement

The effect of Dayvigo® on middle of the night safety was assessed in a randomized, placebo- and active-controlled study that included healthy females (≥55 years) or males (≥65 years). Postural stability, the ability to awaken in response to a sound stimulus, and attention and memory were assessed after a scheduled awakening 4 hours after the start of the 8-hour time in bed. Postural stability was measured by assessing body sway using an ataxia meter. Nighttime dosing of Dayvigo® 5mg and 10mg resulted in impairment of balance (measured by body sway area) at 4 hours as compared to placebo. The ability to awaken to sound in the middle of the night was assessed using an audiometer that delivered 1000 Hz tones. There were no meaningful differences between Dayvigo® doses and placebo on ability to awaken to sound.

In addition, a computerized performance assessment battery was administered to assess attention and memory after middle of the night awakening (4 hours post-dose). Dayvigo® was associated with dose-dependent worsening on measures of attention and memory as compared to placebo. Patients should be cautioned about the potential for middle of the night postural instability, as well as in attention and memory impairment.

The effects of Dayvigo® on next day postural stability and memory were assessed in two randomized, placebo- and active-controlled studies that included healthy subjects and insomnia patients age 55 years and older. There were no meaningful differences between Dayvigo® and placebo on next-day postural stability or memory compared to placebo.

A randomized, double-blind, placebo- and active-controlled, 4-period crossover study assessed the effects of nighttime administration of Dayvigo® on next-morning driving performance about 9 hours after dosing in 24 healthy elderly subjects and 24 adult subjects. The primary driving performance outcome measure was change in Standard Deviation of Lateral Position (SDLP). Testing was conducted after one night (a single dose) and after 8 consecutive nights of treatment with Dayvigo®. Although Dayvigo® 5mg and 10mg did not cause statistically significant impairment in next-morning driving performance in adult or elderly subjects compared with placebo, driving ability was impaired in some subjects taking Dayvigo® 10mg.

Rebound insomnia was assessed by comparing sleep diary-recorded sSOL and sWASO from the screening period to the 2 weeks after treatment discontinuation in both studies 1 and 2. Analyses of group means and the proportion of patients with rebound insomnia suggest that Dayvigo® was not associated with rebound insomnia after treatment discontinuation.

In 12-month and 1-month controlled safety and efficacy trials (studies 1 and 2, respectively), withdrawal effects were assessed by the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire after discontinuation from study drug in patients who received Dayvigo® 5mg or 10mg. There was no evidence of withdrawal effects after Dayvigo® discontinuation at either dose.

Place in Therapy: Dayvigo®, an orexin receptor antagonist, is indicated for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. In clinical studies compared with placebo, Dayvigo® 5mg and 10mg demonstrated statistically significant superiority on the primary efficacy of sSOL and LPS as compared with placebo. It also demonstrated statistically significant improvement in secondary outcomes as compared with placebo.

Per the full text head-to-head phase 3 study by Rosenberg et al[2], the active comparator in study 2 was zolpidem tartrate extended release 6.25mg, taken at bedtime for 1 month. Results suggested that the mean decrease from baseline in the log-transformed LPS was significantly greater for both doses of lemborexant therapy at nights 1 and compared with placebo and zolpidem therapy (least squares geometric means [LSGM] ratio vs zolpidem for lemborexant 5mg was 0.87, p=0.02; and for lemborexant 10mg was 0.82, p<0.001). This effect of lemborexant was maintained after 1 month treatment, with a significant mean decrease from baseline in the log-transformed LPS observed for both doses of lemborexant therapy compared with placebo and zolpidem therapy (LSGM treatment ratio vs zolpidem for lemborexant 5mg was 0.63, p<0.001; and for lemborexant 10mg was 0.59, p<0.001) at nights 29 and 30. Note that zolpidem extended release, the active comparator, was dosed only at 6.25 mg despite being available as a 12.5mg tablet that was not included in the study. The overall incidence of treatment-emergent adverse events was similar among treatment groups.

There is some evidence from a phase 3 study to suggest that Dayvigo® may be more effective than zolpidem extended release 6.25mg, though this is a relatively low dose for this comparator drug; however, there is no evidence at this time that Dayvigo® is safer or more effective than the other currently preferred medications. It is therefore recommended that Dayvigo® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement:
☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Dayvigo [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2020.
[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: A phase 3 randomized clinical trial. *JAMA Netw Open*. 2019; 2(12):e1918254.