Drug Monograph

Drug Name:	**Dayvigo™ (lemborexant) Tablet**
Drug Class:	**Sedative Hypnotics, Non-Benzodiazepines**
Prepared For:	MO HealthNet
Prepared By:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Dayvigo is available in 5 mg and 10 mg oral tablets of lemborexant.
Manufacturer:	Distributed by: Eisai Inc. Woodcliff Lake, NJ 07677
Summary of Findings:	The efficacy of Dayvigo was demonstrated in two clinical trials in patients with insomnia defined as having difficulties with sleep onset and/or maintaining sleep. The first study was a 6-month, randomized, double-blind, placebo-controlled multi-center trial in male and female patients age 18 or older. The primary efficacy endpoint was the mean change of the estimated minutes from the time that the patient attempted to sleep until sleep onset from baseline to end of treatment at 6-months. Those taking Dayvigo 5 mg ($p<0.0001$) or Dayvigo 10 mg ($p<0.0001$) had statistically significant superiority on the primary efficacy measure compared to placebo. The second study was a 1-month, randomized, double-blind, placebo- and active-controlled, multi-center, parallel-group trial in adult female patients age 55 or older and male patients age 65 or older. The primary efficacy endpoint was the mean change in the number of minutes from lights off to the first 10 consecutive minutes of non-wakefulness from baseline to end of treatment (Days 29/30). Those taking Dayvigo 5 ($p<0.0003$) mg or Dayvigo 10 mg ($p<0.0001$) had statistically significant superiority on the primary efficacy measure compared to placebo.
Status Recommendation:	☐ Clinical Edit ☐ PA Required ☐ Open Access ☒ PDL
Type of PA Criteria:	☐ Appropriate Indications ☒ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2,3]

Insomnia, or difficulty in falling asleep or staying asleep, is one of the most common sleep disorders. The National Institutes of Health estimates that about 30% of the general population complains of sleep disruption and about 10% have associated symptoms of daytime functional impairment consistent with the diagnosis of insomnia. There are many types of insomnia with the two most common being acute and chronic insomnia. Acute insomnia is a brief episode of difficulty in sleeping that is usually caused by a stressful life-changing event such as switching careers or receiving bad news. Chronic insomnia is a long-term pattern of difficulty in falling asleep or staying asleep for at least three nights per week for three months or longer.

Dosage Form [1]

Dayvigo is available in a 5 mg and 10 mg oral tablet of lemborexant.

Manufacturer [1]

Distributed by: Eisai Inc. Woodcliff Lake, NJ 07677

Indication(s) [1]

Dayvigo is indicated for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Clinical Efficacy [1,4,5,6] (mechanism of action/pharmacology, comparative efficacy)

Dayvigo's mechanism of action is assumed to be through the antagonism of orexin receptors. The orexin neuropeptide signaling plays a role in wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is believed to prevent people from staying awake.

Pharmacokinetics:

Absorption	Time to peak: 1 to 3 hours
Metabolism	Hepatic metabolism primarily by CYP3A4 and to a lesser extent by CYP3A5, the major circulating active metabolite is M10
Excretion	Feces: 57.4% Urine: 29.1% (<1% as unchanged)
Half-life	17 (5 mg dose) to 19 hours (10 mg dose)

Clinical Trials Experience

STUDY 1 DESIGN (SUNRISE 2)	Long-term, multi-center, randomized, double-blind, placebo-controlled, parallel group

INCLUSION CRITERIA	• Male or female, age 18 years or older at the time of informed consent
	• Meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5) criteria for Insomnia Disorder, as follows:
	  ○ Complains of dissatisfaction with nighttime sleep in the form of difficulty getting to sleep, difficulty staying asleep, and/or awakening earlier in the morning than desired despite adequate opportunity for sleep
	  ○ Frequency of complaint ≥3 times per week
	  ○ Duration of complaint ≥3 months
	  ○ Associated with complaint of daytime impairment
	• History of subjective Sleep Onset Latency (sSOL) ≥30 minutes on at least 3 nights per week in the previous 4 weeks and/or subjective Wake after Sleep Onset (sWASO) ≥60 minutes on at least 3 nights per week in the previous 4 weeks
	• History of regular time spent in bed, either sleeping or trying to sleep, between 7 and 9 hours
	• Regular bedtime, between 21:00 and 01:00 and regular wake time, the time the participant gets out of bed for the day, between 05:00 and 10:00
	• Insomnia Severity Index (ISI) score ≥15
	• Confirmation of current insomnia symptoms as determined from the Sleep Diary completed on at least 7 consecutive mornings (minimum 5 of 7 for eligibility), such that sSOL ≥30 minutes on at least 3 of the 7 nights and/or sWASO ≥60 minutes on at least 3 of the 7 nights
	• Confirmation of time spent in bed, as determined from the Sleep Diary completed on 7 mornings between the first and second screening visit, such that there are not more than 2 nights with duration of time spent in bed between 7 hours and 10 hours
	• Confirmation of regular bedtimes and wake times such that the participant has a regular time spent in bed, either sleeping or trying to sleep, between 7 and 10 hours for the final 7 nights of the week before visit 3.
	• Confirmation of regular bedtime between 21:00 and 01:00 and time of getting out of bed for the day between 05:00 and 10:00 for the final 7 nights of the week before visit 3.
	• Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night
	• Willing to not start a behavioral or other treatment program for insomnia during the participants' participation in the study

EXCLUSION CRITERIA	• A current diagnosis of sleep-related breathing disorder, periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or an exclusionary score on screening instruments to rule out individuals with symptoms of certain sleep disorders other than insomnia. ○ STOPBang score ≥ 5

	○ International Restless Legs Scale (IRLS) score ≥16 ○ Epworth Sleepiness Scale (ESS) score >15 • Reports symptoms potentially related to narcolepsy that in the clinical opinion of the investigator indicates the need for referral for a diagnostic evaluation for the presence of narcolepsy • Reports a history of sleep-related violent behavior, or sleep driving, or any other complex sleep-related behavior, eg, making phone calls, or preparing and eating food while asleep • Beck Depression Inventory - II (BDI II) score >19 • Beck Anxiety Inventory (BAI) score >15 • Habitually naps more than 3 times per week • Females who are breastfeeding or pregnant at screening or at study baseline • Females of childbearing potential who are not practicing acceptable pregnancy prevention methods (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal or have been sterilized surgically.) • Excessive caffeine use that in the opinion of the investigator contributes to the participant's insomnia, or habitually consumes caffeine-containing beverages after 18:00 and is unwilling to forego caffeine after 18:00 for the duration of his/her participation in the study • History of drug or alcohol dependency or abuse within approximately the previous 2 years • Reports habitually consuming more than 14 drinks containing alcohol per week (females) or more than 21 drinks containing alcohol per week (males), or unwilling to limit alcohol intake to no more than 2 drinks per day or forego having alcohol within the 3 hours before bedtime for the duration of his/her participation in the study • A prolonged QT/QT interval corrected by Fridericia's formula (QTcF >450 ms) as demonstrated by a repeated electrocardiogram (ECG) at screening (repeated only if initial ECG indicates a QTcF interval >450 ms) • Current evidence of clinically significant disease (e.g., cardiac, respiratory, gastrointestinal, renal, neurological [including participants who lack capacity and/or whose cognitive decline indicates disorientation to person/place/time and/or situation], or psychiatric disease or malignancy other than basal cell carcinoma) or chronic pain that in the opinion of the investigator could affect the participant's safety or interfere with the study assessments • Comorbid nocturia resulting in frequent need to get out of bed to use the bathroom during the night • Scheduled for major surgery during the study • Used any prohibited prescription or over-the-counter concomitant medications within 1 week before the first dose of study medication • Used any modality of treatment for insomnia, including cognitive behavioral therapy or marijuana within 2 weeks before screening

	• Failed treatment with suvorexant (Belsomra®) (efficacy and/or safety) following treatment with an appropriate dose and adequate duration in the opinion of the investigator • Transmeridian travel across more than 3 time zones in the 2 weeks before screening, or between screening and study baseline • Previously participated in any clinical trial of Dayvigo
TREATMENT REGIMEN	971 participants were randomized to receive Dayvigo 5 mg (n=323), Dayvigo 10 mg (n=323), or placebo (n=325) each taken orally in tablet form at home each night immediately before the time participant intends to sleep for 2 periods of 6 months each. Those in the placebo group received the placebo for period 1 and then re-randomized to Dayvigo 5 mg or Dayvigo 10 mg for period 2.
RESULTS	Primary efficacy endpoint was the mean change from baseline to end of treatment of 6-months for log-transformed patient-reported sSOL Those taking Dayvigo 5 mg had a baseline mean of 43.0 minutes to a 6-month mean of 20 minutes. Those taking Dayvigo 10 mg had a baseline mean of 45.0 minutes to a 6-month mean of 19.2 minutes. Those taking placebo had a baseline mean of 45.0 minutes to a 6-month mean of 27.3 minutes.
SAFETY	Discussed in the Adverse Effects section below.

STUDY 2 DESIGN (SUNRISE 1)	Multi-center, randomized, double-blind, placebo-controlled, active comparator, parallel-group

INCLUSION CRITERIA	• Male age 65 or older or female age 55 or older at the time of informed consent
	• Meets the DSM 5, as follows:
	  ○ Complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep (Note that if the complaint is limited to difficulty initiating sleep, the participant is not eligible)
	  ○ Frequency of complaint ≥ 3 times per week
	  ○ Duration of complaint ≥ 3 months
	  ○ Associated with complaint of daytime impairment
	• History of sWASO typically ≥ 60 minutes on at least 3 nights per week in the previous 4 weeks
	• Reports regular time spent in bed, either sleeping or trying to sleep, between 7 and 9 hours
	• Reports habitual bedtime, defined as the time the participant attempts to sleep, between 21:00 and 24:00 and habitual waketime between 05:00 and 09:00
	• ISI score ≥ 13
	• Confirmation of current insomnia symptoms as determined from responses on the Sleep Diary before the second screening visit
	• Confirmation of regular bedtime and waketime as determined from responses on the Sleep Diary
	• Confirmation of sufficient duration of time spent in bed, as determined from responses on the Sleep Diary

	• Objective (polysomnography [PSG]) evidence of insomnia as follows: sWASO average ≥ 60 minutes on the 2 consecutive PSGs, with neither night < 45 minutes • Willing and able to comply with all aspects of the protocol, including staying in bed for at least 7 hours each night • Willing not to start a behavioral or other treatment program for the treatment of insomnia during the participant's participation in the study
EXCLUSION CRITERIA	• A current diagnosis of sleep-related breathing disorder including obstructive sleep apnea (with or without continuous positive airway pressure [CPAP] treatment), periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorder, or narcolepsy, or an exclusionary score on screening instruments to rule out individuals with symptoms of certain sleep disorders other than insomnia as follows: o STOPBang score ≥5 o International Restless Legs Scale score ≥16 o Epworth Sleepiness Scale score >15 • Reports symptoms potentially related to narcolepsy, that in the clinical opinion of the investigator indicates the need for referral for a diagnostic evaluation for the presence of narcolepsy • On the Munich Parasomnia Scale (MUPS), endorsed the item that corresponds to a history of sleep-eating or reports a history of sleep-related violent behavior, sleep-driving, or symptoms of another parasomnia that in the investigator's opinion make the participant unsuitable for the study • Apnea-Hypopnea Index > 15 or Periodic Limb Movement with Arousal Index >15 as measured on the PSG at the second screening visit • BDI-II score >19 at screening • BAI score >15 at screening • Habitually naps during the day more than 3 times per week • Is a female of childbearing potential Note: All females will be considered to be of childbearing potential unless they are postmenopausal (defined as amenorrheic for at least 12 consecutive months, and are postmenopausal without other known or suspected cause), or have been sterilized surgically (i.e., bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing). • Excessive caffeine use that in the opinion of the investigator contributes to the participant's insomnia, or habitually consumes caffeine-containing beverages after 18:00 and is unwilling to forego caffeine after 18:00 for the duration of his/her participation in the study. • History of drug or alcohol dependency or abuse within approximately the previous 2 years • Reports habitually consuming more than 14 drinks containing alcohol per week (females) or more than 21 drinks containing alcohol per week (males), or unwilling to limit alcohol intake to no more than 2 drinks per day or forego having alcohol within the 3

	hours before bedtime for the duration of his/her participation in the study • Known to be positive for human immunodeficiency virus • Active viral hepatitis (B or C) as demonstrated by positive serology at screening • A prolonged QT/QTcF interval (QTcF >450 milliseconds [ms]) as demonstrated by a repeated ECG at screening (repeated only if initial ECG indicates a QTcF interval >450 ms) • Current evidence of clinically significant disease (e.g., cardiac; respiratory including chronic obstructive pulmonary disease, acute and/or severe respiratory depression; gastrointestinal; severe hepatic impairment; renal including severe renal impairment; neurological including myasthenia gravis; psychiatric disease; or malignancy within the past 5 years other than adequately treated basal cell carcinoma) or chronic pain that in the opinion of the investigator(s) could affect the participant's safety or interfere with the study assessments, including the ability to perform tasks on the cognitive performance assessment battery (PAB). Participants for whom a sedating drug would be contraindicated for safety reasons because of the participant's occupation or activities are also excluded. • Comorbid nocturia resulting in frequent need to get out of bed to use the bathroom during the night • Any history of a medical or psychiatric condition that in the opinion of the investigator(s) could affect the participant's safety or interfere with the study assessment, including the ability to perform the PAB. • Any suicidal ideation with intent with or without a plan, at the time of or within 6 months before the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) administration during the Pre-randomization Phase (i.e., answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the eC-SSRS) • Any suicidal behavior in the past 10 years (per the Suicidal Behavior section of the eC-SSRS) • Scheduled for surgery during the study • Used any prohibited prescription or over-the-counter concomitant medications within 1 week or 5 half-lives, whichever is longer, before the first dose of study medication (run-in period). • Used any modality of treatment for insomnia, including cognitive behavioral therapy or marijuana within 1 week or 5 half-lives, whichever is longer, before the first dose of study medication (run-in period) • Failed treatment with Belsomra (efficacy and/or safety) following treatment with an appropriate dose and of adequate duration in the opinion of the investigator • Transmeridian travel across more than 3 time zones in the 2 weeks before screening, or between screening and baseline, or plans to travel across more than 3 time zones during the study • A positive drug test at screening, run-in, or baseline, or unwilling to refrain from use of recreational drugs during the study

	• Hypersensitivity to Dayvigo or zolpidem or to their excipients • Currently enrolled in another clinical trial or used any investigational drug or device within 30 days or 5× the half-life, whichever is longer preceding informed consent • Previously participated in any clinical trial of Dayvigo
TREATMENT REGIMEN	1006 participants were randomized to receive one Dayvigo 5 mg tablet and one zolpidem-matched placebo tablet (n=266), one Dayvigo 10 mg tablet and one zolpidem-matched placebo tablet (n=269), one zolpidem tartrate 6.25 mg and one Dayvigo-matched placebo tablet (n=263), or one zolpidem-matched placebo tablet and one Dayvigo-matched placebo tablet (n=208); with each set of two tablets taken orally at home each night immediately before the time participant intends to try to fall sleep for 1 month.
RESULTS	Primary efficacy endpoint was the mean change in log-transformed latency to persistent sleep (LPS) from baseline to end of treatment (Day 29/30) defined as the number of minutes from lights off to the first 10 consecutive minutes of non-wakefulness. Those taking the Dayvigo 5 mg set had a baseline mean of 33.0 minutes and a Day 29/30 mean of 15.5 minutes. Those taking the Dayvigo 10 mg set had a baseline mean of 33.3 minutes and a Day 29/30 mean of 14.5 minutes. Those the taking placebo set had a baseline mean of 33.6 minutes and a Day 29/30 mean of 20.0 minutes.
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [(1)]

Dayvigo is contraindicated in patients with narcolepsy.

Warnings and Precautions [(1)]

- CNS depressant effects and daytime impairment
  - Impairs alertness and motor coordination including morning impairment
  - Risk increases with dose and use with other CNS depressants
  - Next-day driving and other activities requiring complete mental alertness is not recommended in those taking Dayvigo 10 mg
- Sleep paralysis, hypnogogic/hypnopompic hallucinations and cataplexy-like symptoms
- Complex sleep behaviors
  - Include: sleep-walking, sleep-driving, and other activities while not full awake
  - Discontinue use of Dayvigo if these behaviors occur
- Compromised respiratory function
- Worsening of depression and/or suicidal ideation
  - Prescribe lowest number of tablets to avoid intentional overdose
- Reevaluate for co-morbid diagnoses if insomnia persists after 7 to 10 days of treatment

Adverse Effects [(1)]

Most common, ≥ 2 %	Dayvigo 5 mg (n = 580) %	Dayvigo 10 mg (n = 580) %	Placebo (n = 528) %
Somnolence or fatigue*	6.9	9.6	1.3
Headache	5.9	4.5	3.4

Nightmare or abnormal dreams	0.9	2.2	0.9

*Combines preferred terms somnolence, lethargy, fatigue, sluggishness

Drug Interactions [1]

- Strong or moderate CYP3A4 inhibitors: Avoid concomitant use.
- Strong or moderate CYP3A4 inducers: Avoid concomitant use.
- Weak CYP3A45 inhibitors: Maximum recommended daily dose of 5 mg.

Dosage and Administration [1]

The recommended dose is 5 mg taken no more than once per night immediately before going to bed, with at least 7 hours remaining before the planned time of awakening. Dosing may be increased to the maximum recommended dose of 10 mg based on clinical response and tolerability. Time to sleep onset may be delayed if taken with or close after a meal. Those with moderate hepatic impairment are recommended to an initial and maximum recommended dose of 5 mg once per night. Those with severe hepatic impairment are not recommended to take Dayvigo.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/Month
Lemborexant	Dayvigo	Eisai Inc.	5 mg, 10 mg	$275.00
Suvorexant	Belsomra	Merck & Co., Inc.	5 mg, 10 mg, 15 mg, 20 mg	$365.70

** Wholesale Acquisition Cost

Conclusion

Dayvigo is indicated for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. It is recommended to only take Dayvigo when at least 7 hours remain before the planned time of awakening and not with or soon after a meal. The efficacy of Dayvigo was demonstrated in two clinical trials. The first study evaluated 971 patients age 18 years or older to determine the mean change of the estimated minutes from the time that the patients collectively attempted to sleep until sleep onset from baseline to end of treatment at 6-months. The second study evaluated 1006 patients age 55 years or older to determine the mean change in the number of minutes from lights off to the first 10 consecutive minutes of non-wakefulness from baseline to end of treatment (Days 29/30). The overall results of both trials were statistically significant in favoring those taking Dayvigo 5 mg or Dayvigo 10 mg having better treatment success in improved symptoms of insomnia as compared to those taking a placebo. The most common adverse effects with Dayvigo use were somnolence or fatigue, headache, and nightmare or abnormal dreams.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL).

References

1) Dayvigo: Package Insert. 2019. Available from: www.accessdata.fda.gov. Accessed June 8,

2020.
2) National Sleep Foundation. Insomnia. Available at: sleepfoundation.org. Accessed June 8, 2020.
3) American Sleep Association. Insomnia. Available at: sleepassociation.org. Accessed June 8, 2020.
4) Dayvigo: Drug Information. Lexi-Drugs. Wolters Kluwer Clinical Drug Information Inc.
5) Long-term study of lemborexant in insomnia disorder (SUNRISE 2). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT02952820
6) Study of the efficacy and safety of lemborexant in subjects 55 years and older with insomnia disorder (SUNRISE 1). Clinical Trials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT02783729

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