PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]DAYVIGO™

Lemborexant Tablet

Tablet, 5 mg, 10 mg, Oral

House Standard

Hypnotic

ATC Code: N05CM21

Eisai Limited

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Date of Initial Authorization:
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RECENT MAJOR LABEL CHANGES

Section 7 WARNINGS AND PRECAUTIONS, Respiratory	06/2023
Section 7.1.2 Breast-feeding	06/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DAYVIGO™ (lemborexant) is indicated for:

- the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

1.1 Pediatrics

Pediatrics (< 18 years of age): The safety and effectiveness of DAYVIGO in pediatric patients have not been established. Therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No clinically meaningful differences in safety or effectiveness were observed between patients ≥ 65 years of age and younger patients at the recommended doses (see 7.1.4 Geriatrics and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

2 CONTRAINDICATIONS

DAYVIGO is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with narcolepsy.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Time to sleep onset may be delayed if taken with or soon after a meal (see 9.5 Drug-Food Interactions and 10.3 Pharmacokinetics, Absorption).
- Patients should be advised not to consume alcohol in combination with DAYVIGO (see 9.2 Drug Interactions Overview, Alcohol and 10.2 Pharmacodynamics, Alcohol).

4.2 Recommended Dose and Dosage Adjustment

Use the lowest effective dose for the patient.

The recommended dose of DAYVIGO is 5 mg, taken no more than once per night and within a few minutes 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 10 mg based on clinical response and tolerability.

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 10.3 Pharmacokinetics, Special Populations and Conditions, Pediatrics).

Geriatrics (≥ 65 years of age): No dose adjustment is required in geriatric patients (see 7.1.4 Geriatrics and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

Patients with Hepatic Impairment: No dose adjustment is required in patients with mild hepatic impairment. The maximum recommended dose of DAYVIGO is 5 mg no more than once per night in patients with moderate hepatic impairment. DAYVIGO is not recommended in patients with severe hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic and 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

Patients with Renal Impairment: No dose adjustment is required in patients with renal impairment (see 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

Use with CYP3A Inhibitors and Inducers: Avoid concomitant use of DAYVIGO with moderate or strong CYP3A inhibitors. The maximum recommended dose of DAYVIGO is 5 mg no more than once per night when co-administered with weak CYP3A inhibitors (see 9.2 Drug Interactions Overview, Potential for Other Medicinal Products to Affect DAYVIGO, CYP3A Inhibitors and 9.4 Drug-Drug Interactions, Effect of Other Drugs on DAYVIGO).

Co-administration of DAYVIGO with CYP3A inducers is not recommended due to the potential for a decrease in DAYVIGO efficacy (see 9.2 Drug Interactions Overview, Potential for Other Medicinal Products to Affect DAYVIGO, CYP3A Inducers and 9.4 Drug-Drug Interactions, Effect of Other Drugs on DAYVIGO).

Use with CNS Depressants: When DAYVIGO is combined with CNS depressant drugs, dosage adjustment of DAYVIGO and/or the other drug(s) may be necessary because of potentially additive effects (See 7 WARNINGS AND PRECAUTIONS, General, CNS Depressant Effects and Daytime Impairment and 9.2 Drug Interactions Overview, CNS-active Agents).

4.5 Missed Dose

If a patient misses a dose, the patient should be instructed not to take DAYVIGO unless there is an opportunity to sleep for at least 7 hours before being active again.

They may continue with their usual dose the following night.

5 OVERDOSAGE

There is limited clinical experience with DAYVIGO overdose. In clinical pharmacology studies, healthy patients who were administered multiple doses of up to 75 mg per day of DAYVIGO showed dose-dependent increases in the frequency of somnolence.

General symptomatic and supportive measures should be used. Intravenous fluids should be administered as needed. As in all cases of drug overdose, vital signs should be monitored, and general supportive measures employed. The value of dialysis in the treatment of overdosage has not been determined. As DAYVIGO is highly protein-bound, hemodialysis is not expected to contribute to elimination of DAYVIGO.

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. Consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdosage.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients

Oral	film-coated tablets
	5 mg lemborexant
	10 mg lemborexant
		• hydroxypropyl cellulose
		• lactose monohydrate
		• low-substituted hydroxypropyl cellulose
		• magnesium stearate
		• film coating: contains hypromellose 2910, polyethylene glycol 8000, talc, titanium dioxide, and
		  • for the 5 mg tablet: ferric oxide yellow
		  • for the 10 mg tablet: ferric oxide yellow and ferric oxide red.

- DAYVIGO 5 mg film-coated tablets are: pale yellow, round, biconvex, and debossed with "5" on one side and "LEM" on the other side.
- DAYVIGO 10 mg film-coated tablets are: orange, round, biconvex, and debossed with "10" on one side and "LEM" on the other side.

DAYVIGO film-coated tablets are packaged in bottles of 30 or 90

7 WARNINGS AND PRECAUTIONS

General

CNS Depressant Effects and Daytime Impairment

Hypnotics including DAYVIGO may impair daytime wakefulness even when used as prescribed. Co-administration with CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression, which can cause daytime impairment. Dosage adjustments of DAYVIGO and of concomitant CNS depressants may be necessary when administered together because of potentially additive effects. The use of DAYVIGO with other drugs to treat insomnia is not recommended (see 9.2 Drug Interactions Overview, CNS-active Agents).

Patients should be advised not to consume alcohol in combination with DAYVIGO because of additive effects (see 9.2 Drug Interactions Overview, Alcohol).

The risk of daytime impairment, including impaired driving, is increased if DAYVIGO is taken with less than a full night (at least 7 hours) 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 requiring complete mental alertness (see 10.2 Pharmacodynamics, Special Safety Studies,

Effects on Driving and 7 WARNINGS AND PRECAUTIONS, Driving and Operating Machinery.

Because DAYVIGO can cause drowsiness, patients, particularly the elderly, may be at a higher risk of falls.

CNS depressant effects may persist in some patients for up to several days after discontinuing DAYVIGO. The lowest effective dose for the patient should be used (see 4.2 Recommended Dose and Dosage Adjustment, Use with CNS Depressants).

Complex Sleep Behaviours

Complex sleep behaviours such as "sleep-driving" (i.e., driving while not fully awake after taking a hypnotic) and other complex behaviours (e.g., preparing and eating food, making phone calls, leaving the house or having sex), with amnesia for the event, have been reported in association with the use of hypnotics such as DAYVIGO. These events can occur in hypnotic-naïve as well as in hypnotic-experienced persons. Although complex sleep-related behaviours may occur with DAYVIGO alone at therapeutic doses, the use of alcohol and other CNS depressants may increase the risk of such behaviours.

While complex sleep-related behaviours have been reported in patients with or without history of sleepwalking, it is possible that some predisposed patients are at increased risk of experiencing these complex behaviours during treatment with DAYVIGO. Patients with other disorders known to affect sleep and induce frequent awakenings (e.g. sleep apnea, Periodic Limb Movement Disorder, Restless Legs Syndrome) may be also at increased risk of complex sleep-related behaviours.

Due to the risk to the patient and the community, discontinue DAYVIGO immediately if a patient experiences a complex sleep-related behaviour.

Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms

Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, and hypnagogic/hypnopompic hallucinations, including vivid and disturbing perceptions, can occur with the use of DAYVIGO. Prescribers should explain the nature of these events to patients when prescribing DAYVIGO.

Symptoms similar to mild cataplexy can occur with DAYVIGO. Such symptoms can include periods of leg weakness lasting from seconds to a few minutes, can occur either at night or during the day, and may not be associated with an identified triggering event (e.g., laughter or surprise).

Need to Evaluate for Co-Morbid Diagnoses

Because sleep disturbances may be the presenting manifestation of a medical and/or psychiatric disorder, treatment of insomnia should be initiated only after careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new cognitive or behavioural abnormalities may be the result of an unrecognized underlying psychiatric or medical disorder and can emerge during the course of treatment with sleep-promoting drugs such as DAYVIGO.

Drug Interactions - Inhibitors of CYP3A

Concomitant use of DAYVIGO with moderate or strong CYP3A inhibitors is not recommended (see 4.2 Recommended Dose and Dosage Adjustment, Use with CYP3A Inhibitors and Inducers and 9.2 Drug-Interactions Overview, Potential for Other Medicinal Products to Affect DAYVIGO, CYP3A Inhibitors).

Lactose

Lactose is a non-medicinal ingredient in DAYVIGO. Patients with rare hereditary diseases of galactose intolerance (galactosemia or glucose-galactose malabsorption) should not take DAYVIGO.

Dependence/Tolerance

As with other hypnotics, care should be taken when prescribing DAYVIGO to individuals with a history of addiction to, or abuse of, drugs or alcohol due to risk of misuse or abuse.

Abuse

In human abuse liability study conducted in recreational sedative users (n=39), DAYVIGO (10, 20, and 30 mg) produced similar responses on positive subjective measures such as "Drug Liking", "Overall Drug Liking", "Take Drug Again", and "Good Drug Effects" as zolpidem (30 mg) and suvorexant (40 mg), which were statistically significantly greater than placebo. Because 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.

Dependence

In completed clinical trials with DAYVIGO, there was no clear evidence for physical dependence or withdrawal symptoms with the prolonged use of DAYVIGO as assessed by the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire.

Rebound Insomnia

Rebound insomnia was assessed following discontinuation of DAYVIGO relative to placebo and baseline in both elderly and non-elderly adult patients receiving DAYVIGO 5 mg or 10 mg after 1 month and 1 year. No statistically significant effects were seen on measures of sleep onset latency or time awake after sleep onset in comparison to baseline values or relative to placebo.

Driving and Operating Machinery

DAYVIGO may impair driving skills and decrease mental alertness. Discontinue or decrease the dose to 5 mg in patients who drive or operate machinery if daytime somnolence develops. 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 (see 7 WARNINGS AND PRECAUTIONS, General, CNS Depressant Effects and Daytime Impairment). If DAYVIGO is taken in these circumstances, patients should be cautioned against driving and other activities requiring complete mental alertness.

In a study designed to evaluate the effects of nighttime administration of DAYVIGO on next-morning driving performance approximately 9 hours after dosing, there was no statistically significant impairment compared with placebo in driving performance in adult and elderly patients given DAYVIGO at either 5 mg or 10 mg (see 10.2 Pharmacodynamics, Special Safety Studies, Effects on Driving). However, driving ability was impaired in some subjects taking DAYVIGO 10 mg.

Hepatic/Biliary/Pancreatic

DAYVIGO has not been studied in patients with severe hepatic impairment. Use in this population is not recommended (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Hepatic Impairment

and 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

DAYVIGO exposure (AUC and C_{max}) and terminal half-life were increased in patients with moderate hepatic impairment (Child-Pugh class B). The maximum recommended dose of DAYVIGO is 5 mg no more than once per night in patients with moderate hepatic impairment (Child-Pugh class B) (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Hepatic Impairment).

DAYVIGO exposure (AUC) was increased in patients with mild hepatic impairment (Child-Pugh class A), but the terminal half-life was not changed. Patients with mild hepatic impairment may experience an increased risk of somnolence (see 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

Psychiatric

Abnormal Thinking and Behavioural Changes

A variety of cognitive and behavioural changes (e.g., memory loss (amnesia), anxiety, hallucinations and other neuro-psychiatric symptoms) have been reported to occur in association with the use of hypnotics such as DAYVIGO.

Worsening of Depression/Suicidal Ideation

In clinical studies of DAYVIGO in patients with insomnia, the incidence of suicidal ideation or any suicidal behaviour, as assessed by questionnaire, was higher in patients receiving DAYVIGO than in those receiving placebo (0.3% for DAYVIGO 10 mg, 0.4% for DAYVIGO 5 mg, and 0.2% for placebo).

In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions (including completed suicides) 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; therefore, the lowest number of tablets that is feasible should be prescribed at any one time.

Patients, their families, and their caregivers should be encouraged to be alert to worsening of depression, including suicidal thoughts and actions. Such symptoms should be reported to the patient's prescriber or health professional. The emergence of any new behavioural sign or symptom of concern requires careful and immediate evaluation.

Reproductive Health: Female and Male Potential

- **Fertility**

Effects on fertility have been observed in female rats at the doses of 100 mg/kg/day and 1000 mg/kg/day. Irregular estrous cycle and decreased pregnancy rate were observed at 100 and 1000 mg/kg/day and decreased numbers of corpora lutea, implantations, and live embryos were noted at 1000 mg/kg/day (see 16 NON-CLINICAL TOXICOLOGY).

- **Teratogenic Risk**

In studies where lemborexant was administered to pregnant rats during organogenesis at oral doses of 60, 200, and 600 mg/kg/day or 20, 60, and 200 mg/kg/day, embryotoxicity and malformations were observed at 600 mg/kg in the presence of maternal toxicity. The maternal exposure at the no observed adverse effect level (NOAEL) (200 mg/kg) was approximately 143 times the exposure at the MRHD based on AUC.

Oral administration of lemborexant to pregnant rabbits during organogenesis at doses of 10, 30, and 100 mg/kg resulted in a higher incidence of skeletal variations at a dose of 100 mg/kg/day, which provided maternal exposures approximately 139 times the exposure at the MRHD based on AUC, but no embryotoxicity or malformations were observed in rabbits (see 7.1.1 Pregnant Women).

Respiratory

Patients with Compromised Respiratory Function

Effects of DAYVIGO on respiratory function should be considered if prescribed to patients with compromised respiratory function.

Obstructive Sleep Apnea

In a placebo-controlled, two-period crossover study of 37 patients with mild obstructive sleep apnea (OSA; apnea-hypopnea index <15 events per hour of sleep) who were treated with DAYVIGO 10 mg, DAYVIGO did not increase the frequency of apneic events or decrease mean peripheral capillary oxygen saturation. In a placebo-controlled, two-period crossover study of 33 patients with moderate or severe OSA (apnea-hypopnea index ≥15 events per hour of sleep) who were treated with DAYVIGO 10 mg once daily for 8 consecutive nights, the mean treatment difference (DAYVIGO – placebo) in the apnea-hypopnea index was not significant [- 0.80 (95% CI, -4.88 to 3.29)]. DAYVIGO did not decrease peripheral capillary oxygen saturation.

Due to study limitations, including the short duration of the study, clinically meaningful respiratory effects of DAYVIGO in obstructive sleep apnea cannot be excluded.

Chronic Obstructive Pulmonary Disease

In a placebo-controlled, two-period crossover study of 30 patients with moderate or severe chronic obstructive pulmonary disease (COPD; Forced expiratory volume in the first second (FEV1)/Forced vital capacity (FVC) ratio ≤ 70% and 30% ≤ FEV1 < 80% of predicted) who were treated with DAYVIGO 10 mg once daily for 8 consecutive nights, the mean treatment difference (DAYVIGO – placebo) in the mean peripheral capillary oxygen saturation was a small significant increase [0.47 (95% CI: 0.07 to 0.87)].

DAYVIGO has not been studied in COPD patients with a FEV1 < 30% of predicted.

Clinically meaningful respiratory effects of DAYVIGO in COPD cannot be excluded.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women. DAYVIGO should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus (see 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential, Teratogenic risk).

Animal data

Administration of lemborexant to pregnant rats during organogenesis in 2 separate studies at oral doses of 60, 200, and 600 mg/kg/day or 20, 60, and 200 mg/kg/day resulted in growth delays at the dose of 600 mg/kg/day, which provided maternal plasma exposures that were approximately 388 times

the plasma exposure at the maximum recommended human dose (MRHD) based on AUC. Embryotoxicity and malformations were observed at 600 mg/kg in the presence of maternal toxicity. The maternal exposure at the no observed adverse effect level (NOAEL) (200 mg/kg) was approximately 143 times the exposure at the MRHD based on AUC.

Oral administration of lemborexant to pregnant rabbits during organogenesis at doses of 10, 30, and 100 mg/kg resulted in a higher incidence of skeletal variations at a dose of 100 mg/kg/day, which provided maternal exposures approximately 139 times the exposure at the MRHD based on AUC, but no embryotoxicity or malformations were observed in rabbits. The exposure at the NOAEL (30 mg/kg) was 23 times the exposure at the MRHD based on AUC.

Oral administration of lemborexant (30, 100, and 300 mg/kg/day) to pregnant rats during gestation and lactation resulted in decreased body weights, femur length, and acoustic startle responses in offspring. The exposure at the NOAEL (100 mg/kg) was 93 times the exposure at the MRHD based on AUC.

7.1.2 Breast-feeding

A milk-only lactation study conducted in 8 lactating women who received a single 10 mg lemborexant dose showed the presence of lemborexant in human milk. The relative infant dose (RID) was on average 2% of the maternal dose. The mean calculated daily infant oral dosage was 0.0029 mg/kg/day based on a nominal infant body weight of 6 kg. Data following repeated doses are not available (see 10.3 Pharmacokinetics, Special Populations and Conditions, Breast-feeding).

There are no data on the effects of lemborexant on the breastfed infant, or the effects on milk production. Infants exposed to DAYVIGO through breastmilk should be monitored for excessive sedation. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for lemborexant and any potential adverse effects on the breastfed child from lemborexant or from the underlying maternal condition.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety and effectiveness of DAYVIGO in pediatric patients have not been established. Therefore, Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics; 4.2 Recommended Dose and Dosage Adjustment, Pediatrics and 10.3 Pharmacokinetics, Special Populations and Conditions, Pediatrics).

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Of the total number of patients treated with DAYVIGO (n=1417) in controlled Phase 3 studies, 491 patients were 65 years and over, and 87 patients were 75 years and over. There were no clinically meaningful differences in safety or effectiveness observed between patients ≥ 65 years and patients < 65 years of age at the recommended doses. No dose adjustment is required in geriatric patients (see 1.2 Geriatrics; 4.2 Recommended Dose and Dosage Adjustment, Geriatrics and 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Table 2: Patient Exposure to DAYVIGO 5 mg or 10 mg in Study 1 and Study 2

Patients Treated	**DAYVIGO 5 mg**	**DAYVIGO 10 mg**
For ≥ 1 Day (n)	713	705
Mean Age (years)	57.9	58.6
Men (n)	186	176
Women (n)	527	529
For ≥ 6 Months (n)	373	335
Through 12 months (n)	230	204

Most Common Adverse Reactions

In clinical trials of patients with insomnia treated with DAYVIGO 5 mg or 10 mg, the most common adverse reaction (reported in 5% or more of patients treated with DAYVIGO and at a higher rate than placebo) was somnolence (DAYVIGO 5 mg 7%, DAYVIGO 10 mg 11%, placebo 2%). DAYVIGO was associated with a dose-related increase in somnolence.

Adverse Reactions Resulting in Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions for patients treated with 5 mg or 10 mg of DAYVIGO was 4% for 5 mg and 6% for 10 mg compared to 3% for placebo.

The most common adverse reaction leading to discontinuation was somnolence (1% for DAYVIGO 5 mg, 2% for DAYVIGO 10 mg, and 1% for placebo).

In Study 1 and 2, the adverse reaction profile of DAYVIGO in elderly (≥ 65 years) patients (n=491) was consistent with adult patients (n=927).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 3 presents the treatment-emergent adverse events based on the pooled data from the first 30 days of Study 1 (6-month controlled efficacy trial) and Study 2 (1-month controlled efficacy trial) where the incidence was ≥1% in DAYVIGO-treated patients and greater than in placebo-treated patients.

Table 3: Percentage of Patients with Treatment-Emergent Adverse Events by Preferred Term – Incidence ≥ 1% in Any DAYVIGO Treatment Group in Patients with Insomnia and Where the Incidence in the DAYVIGO Group Was More than Placebo from Study 1 and Study 2

	Placebo	DAYVIGO	
MedDRA Preferred Term	**(n=528) n (%)**	**5 mg (n=580) n (%)**	**10 mg (n=582) n (%)**
Gastrointestinal disorders			
Nausea	1 (0.2)	8 (1.4)	4 (0.7)
General Disorders and Administration Site Conditions			
Fatigue	0	12 (2.1)	9 (1.5)
Infections and Infestations			
Nasopharyngitis	5 (0.9)	16 (2.8)	10 (1.7)
Upper respiratory tract infection	5 (0.9)	7 (1.2)	4 (0.7)
Urinary tract infection	6 (1.1)	4 (0.7)	12 (2.1)
Musculoskeletal and connective tissue disorders			
Back pain	3 (0.6)	4 (0.7)	6 (1.0)
Nervous System Disorders			
Headache	21 (4.0)	35 (6.0)	27 (4.6)
Somnolence	7 (1.3)	29 (5.0)	49 (8.4)
Psychiatric Disorders			
Abnormal dreams	4 (0.8)	2 (0.3)	6 (1.0)
Nightmare	2 (0.4)	3 (0.5)	6 (1.0)

Other Adverse Reactions

Sleep Paralysis

Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, can occur with the use of DAYVIGO. In clinical trials of DAYVIGO, sleep paralysis was reported: DAYVIGO 5 mg 1.3% or DAYVIGO 10 mg 1.6% compared to no reports for placebo (see 7 WARNINGS AND PRECAUTIONS, General, Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms).

Hypnagogic Hallucinations

Hypnagogic hallucinations were reported in 0.1% and 0.7% of patients receiving DAYVIGO 5 mg and 10 mg, respectively, compared to no reports for placebo (see 7 WARNINGS AND PRECAUTIONS, General, Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms).

Complex Sleep Behaviours

Two events of complex sleep behaviour were reported, both in patients receiving DAYVIGO 10 mg (see 7 WARNINGS AND PRECAUTIONS, General, Complex Sleep Behaviours).

Seizure

One subject in clinical trials receiving DAYVIGO 25 mg, experienced two events of seizure

approximately 2 hours and 3.5 hours after taking study medication on the same evening. The subject had no prior history of seizure disorder, though it is not clear that the episodes experienced had a causal relationship to DAYVIGO.

8.3 Less Common Clinical Trial Adverse Reactions

The following additional adverse events were reported in patients treated with DAYVIGO 5 mg or 10 mg at an infrequent incidence of <1% and >0.1%, and at a frequency greater than placebo, in patients receiving DAYVIGO based on the pooled data from the first 30 days of the 6-month controlled treatment period (Study 1) and the 1-month controlled efficacy study (Study 2). A causal relationship of these events to DAYVIGO is uncertain.

Cardiac disorders:
arrhythmia, palpitations, ventricular extrasystoles

Ear and labyrinth disorders:
tinnitus, vertigo

Gastrointestinal disorders:
diarrhea, dry mouth, vomiting

General disorders and administration site conditions:
discomfort, feeling abnormal, feeling jittery, hangover, peripheral edema, sluggishness, thirst

Infections and Infestations:
conjunctivitis, pharyngitis, pyuria

Investigations:
blood potassium increased, blood triglycerides increased, electrocardiogram T wave inversion, heart rate increased

Metabolism and nutrition disorders:
increased appetite

Musculoskeletal and connective tissue disorders:
muscular weakness, osteoarthritis

Nervous system disorders:
balance disorder, dizziness postural, dysarthria, dysgeusia, head discomfort, lethargy, poor quality sleep, sedation, sleep paralysis, syncope

Psychiatric disorders:
anxiety, autoscopy, confusional state, depressed mood, emotional disorder, exploding head syndrome, hallucination tactile, hypnagogic hallucination, parasomnia, rapid eye movement sleep abnormal

Renal and urinary disorders:
micturition urgency

Respiratory, thoracic and mediastinal disorders:
cough, hyperventilation, throat clearing

Skin and subcutaneous tissue disorders:
Hyperhidrosis

Vascular disorders:
hypotension

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Not applicable.

8.5 Post-Market Adverse Reactions

Not applicable.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

CNS-active Agents

Patients should be advised against combined use of DAYVIGO with CNS depressants (e.g. alcohol, sedative hypnotics, opioids, tricyclic antidepressants, etc.) because of the potential for additive effects on psychomotor performance. If concomitant use of a CNS depressant is warranted, a dosage adjustment of DAYVIGO and/or the other drug(s) may be necessary (See 7 WARNINGS AND PRECAUTIONS, General, CNS Depressant Effects and Daytime Impairment and 10.2 Pharmacodynamics, Alcohol).

Alcohol

Concomitant use of alcohol increases lemborexant C_{max} and AUC (see 9.3 Drug-Behavioural Interactions. Given the additive effects of alcohol on lemborexant, alcohol should not be consumed with DAYVIGO (see 7 WARNINGS AND PRECAUTIONS, General, CNS Depressant Effects and Daytime Impairment; 4.1 Dosing Considerations).

Potential for Other Medicinal Products to Affect DAYVIGO

CYP3A Inhibitors

DAYVIGO is not recommended when co-administered with moderate CYP3A inhibitors (e.g., fluconazole) or strong CYP3A inhibitors (e.g., itraconazole) (see 4.2 Recommended Dose and Dose Adjustment, Use with CYP3A Inhibitors and Inducers and 9.4 Drug-Drug Interactions, Table 4 Established Drug-Drug Interactions).

The recommended dose of DAYVIGO is 5 mg when co-administered with weak CYP3A inhibitors (see 4.2 Recommended Dose and Dose Adjustment, Use with CYP3A Inhibitors and Inducers and 9.4 Drug-Drug Interactions, Effects of Other Drugs on DAYVIGO; Table *4*).

CYP3A Inducers

Use of CYP3A inducers (e.g., rifampin, carbamazepine, St. John's wort) with lemborexant is not recommended as decreased lemborexant efficacy may result (see 4.2 Recommended Dose and Dose Adjustment; 9.4 Drug-Drug Interactions, Effects of Other Drugs on DAYVIGO; Table *4* Established Drug-Drug Interactions and 9.6 Drug-Herb Interactions).

Potential for Lemborexant to Affect Other Medicinal Products

Substrates of CYP3A or CYP2B6

Lemborexant does not affect the pharmacokinetics of CYP3A substrates as shown by the absence of a drug-drug interaction with midazolam (a CYP3A substrate). Lemborexant weakly induces CYP2B6 based on study with bupropion as a CYP2B6 substrate. Substrates of CYP3A and CYP2B6 can be co-administered with DAYVIGO, however physicians should monitor patients for changes related to reduced efficacy of CYP2B6 substrates (see 9.4 Drug-Drug Interactions, Effects of DAYVIGO on Other Drugs; Table 4 Established Drug-Drug Interactions).

9.3 Drug-Behavioural Interactions

Alcohol

Lemborexant C_{max} and AUC increased by 35% and 70%, respectively, when co-administered with a single dose of alcohol (approximating a blood alcohol concentration of 0.08%). Lemborexant did not affect alcohol concentrations. Given the additive effects of alcohol on lemborexant, alcohol should not be consumed with DAYVIGO (see 7 WARNINGS AND PRECAUTIONS, General, CNS Depressant Effects; 4.1 Dosing Considerations).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4: Established Drug-Drug Interactions

Interacting Drug	Source of Evidence	Effect*	Clinical Comment
Effect of co-administered drugs on lemborexant			
CYP3A Inducers			
Rifampin 600 mg (strong CYP3A inducer)	CT	↓ lemborexant C_{max}: ↓ 92%	Not Recommended

		AUC_{∞}: ↓ 97%	
CYP3A Inhibitors			
Itraconazole 200 mg (strong CYP3A inhibitor)	CT	↑ lemborexant C_{max}: ↑ 36% AUC_{∞}: ↑ 270%	Not Recommended
Fluconazole 200 mg (moderate CYP3A inhibitor)	CT	↑ lemborexant C_{max}: ↑ 62% AUC_{∞}: ↑ 317%	Not Recommended
Fluoxetine (weak CYP3A inhibitor)	PBPK Model	↑ lemborexant C_{max}: ↑ 21% AUC_{∞}: ↑ 77%	Maximum Recommended dose: 5 mg
Alcohol			
Alcohol (Female: 0.6 g/kg, Male: 0.7 g/kg)	CT	↑ lemborexant C_{max}: ↑ 35% AUC_{∞}: ↑ 70%	Not Recommended
Gastric pH Modifier / H2 Blockers			
Famotidine 40 mg	CT	↔ lemborexant C_{max}: ↓ 27% AUC_{∞}: ↔	No Dose Adjustment
Oral Contraceptives			
Ethinyl Estradiol 0.030 mg + Norethindrone 1.5 mg	CT	↔ lemborexant	No Dose Adjustment
Effect of lemborexant on co-administered drugs			
CYP2B6 Substrates			

Bupropion 75 mg			
S-Bupropion	CT	↓ S-bupropion C_{max}: ↓ 50% AUC_{∞}: ↓ 46%	No Dose Adjustment of DAYVIGO Monitor patient response to CYP2B6 substrates and consider increasing the dose if necessary
[S,S]-Hydroxylated Bupropion	CT	↓ [S,S]-hydroxylated bupropion C_{max}: ↓ 17% AUC_{∞}: ↓ 25%	No Dose Adjustment of DAYVIGO Monitor patient response to CYP2B6 substrates and consider increasing the dose if necessary
CYP3A Substrates			
Midazolam 2 mg	CT	↔ midazolam	No Dose Adjustment
Oral Contraceptives			
Ethinyl Estradiol 0.030 mg	CT	↔ ethinyl estradiol AUC_{∞}: ↑13%	No Dose Adjustment
Norethindrone 1.5 mg	CT	↔ norethindrone	No Dose Adjustment

Legends: CT = Clinical Trial; PBPK = physiologically-based pharmacokinetic; C_{max} = maximum concentration; AUC_{∞} = AUC from time 0 to infinity

* ↑ = increase; ↓ = decrease; ↔ = no change

Effects of Other Drugs on DAYVIGO

The effects of other drugs on the pharmacokinetics of DAYVIGO (10 mg) are presented in Table 4 as change relative to lemborexant alone (test/reference). Based on these results, drug interactions between lemborexant and strong CYP3A inducers, strong CYP3A inhibitors, and moderate CYP3A inhibitors are clinically significant. Using a physiologically based pharmacokinetic (PBPK) model, a weak effect is predicted when weak CYP3A inhibitors (e.g., fluoxetine) are co-administered with lemborexant.

Co-administration of an H2 blocker (famotidine) with lemborexant decreased C_{max} by 27% and delayed t_{max} by 0.5 hours, but had no statistically significant effect on overall lemborexant exposure (AUC). A population analysis of Phase 1-3 data also showed no effect of proton pump inhibitors (PPIs) on

apparent clearance of lemborexant. A pooled analysis conducted on patients with a medical history of gastroesophageal reflex disease (GERD) or taking PPIs or H2 blockers in Studies 1 and 2 showed that there was no effect on sleep latency or on safety parameters. Thus DAYVIGO can be co-administered with gastric acid-reducing agents (PPIs or H2 blockers).

Co-administration of an oral contraceptive containing norethindrone (NE) and ethinyl estradiol (EE) with DAYVIGO had no statistically significant effect on lemborexant pharmacokinetics.

Effects of DAYVIGO on Other Drugs

In vitro metabolism studies demonstrated that lemborexant and M10 have a potential to induce CYP3A and a weak potential to inhibit CYP3A and induce CYP2B6. Lemborexant and M10 do not have the potential to inhibit other CYP isoforms or transporters (P-gp, BCRP, BSEP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1, and MATE2-K). Lemborexant is a poor substrate of P-gp, but M10 is a substrate of P-gp. Lemborexant and M10 are not substrates of BCRP, OATP1B1, or OATP1B3. Lemborexant and M10 do not induce CYP2C8, CYP2C9, and CYP2C19 at clinically relevant concentrations, as measured by mRNA expression *in vitro*.

Specific *in vivo* effects of lemborexant (10 mg) on the pharmacokinetics of bupropion, oral contraceptives, and midazolam are presented in Table 4 as a change relative to the interacting drug administered alone (test/reference). Based on these results, drug interactions between lemborexant and CYP2B6 substrates are clinically significant.

Co-administration of an oral contraceptive containing norethindrone (NE) and ethinyl estradiol (EE) with DAYVIGO (10 mg) did not affect the C_{max} and AUC of NE or the C_{max} of EE, and increased AUC of EE by 13%. This latter small change is not considered clinically relevant.

Clinical studies with substrates of CYP3A or CYP2B6: Despite the *in vitro* findings (potential for both induction and inhibition of CYP3A4), lemborexant does not affect the pharmacokinetics of CYP3A substrates (e.g., midazolam). Lemborexant weakly induces CYP2B6 (e.g., bupropion is CYP2B6 substrate). CYP3A and CYP2B6 substrates can be co-administered with lemborexant (see Table 4).

9.5 Drug-Food Interactions

Ingestion of DAYVIGO with a high-fat meal resulted in a slight decrease in the rate of absorption of lemborexant as demonstrated by 23% decrease in C_{max} and delay in t_{max} of 2 hours and 18% increase in total exposure AUC. DAYVIGO may be taken with or without food, however, time to sleep onset may be delayed if taken with or soon after a meal (see 4.1 Dosing Considerations and 10.3 Pharmacokinetics, Absorption).

9.6 Drug-Herb Interactions

Co-administration of DAYVIGO with a CYP3A inducer (e.g., St. John's wort) is not recommended. This may result in a decrease in DAYVIGO efficacy (see 4.2 Recommended Dose and Dosage Adjustment, Use with CYP3A Inhibitors and inducers; 9.2 Drug Interactions Overview, Potential for Other Medicinal Products to Affect DAYVIGO, CYP3A Inducers).

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Lemborexant is a competitive antagonist of both orexin receptors, OX1R and OX2R, with a higher affinity for OX2R. It belongs to the pharmacologic class of orexin receptor antagonists. The orexin neuropeptide signaling system is a central promoter of wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress wake drive.

10.2 Pharmacodynamics

Cardiac Electrophysiology

The potential effects of DAYVIGO on the QTc interval using a high precision analysis were examined with the use of concentration-response modeling of the QTc data. The model was built on a single data set based on 46 healthy adult subjects receiving doses ranging from 2.5 mg to 75 mg once a day for 14 days (n=5-6 per treatment arm receiving lemborexant, n=2 for placebo). The concentration-response relationship was analyzed using a linear mixed-effects model. The model did not predict any clinically relevant effect on the QTc interval at concentrations of lemborexant up to 240 ng/mL.

Alcohol

A statistically significant additive negative effect on cognitive performance was observed up to 6 hours post dose when DAYVIGO 10 mg, administered in the morning, was co-administered with a dose of alcohol (0.6 g/kg for females and 0.7 g/kg for males; approximating a blood alcohol level of .08%). No statistically significant treatment differences in change from baseline in postural stability (as evidenced by body sway) were observed when DAYVIGO was co-administered with alcohol versus alcohol alone at any time point. Alcohol should not be consumed with DAYVIGO (see 7 WARNINGS AND PRECAUTIONS, General, CNS Depressant Effects and Daytime Impairment; 4.1 Dosing Considerations and 9.2 Drug Interactions Overview, Alcohol).

Special Safety Studies

Effects on Driving

A randomized, double-blind, placebo- and active-controlled, four-period crossover study evaluated the effects of nighttime administration of DAYVIGO on next-morning driving performance approximately 9 hours after dosing in 24 healthy elderly patients (≥ 65 years old, median age 67 years; 14 men, 10 women) and 24 adult patients (median age 49 years; 12 men, 12 women). The primary driving performance outcome measure was change in Standard Deviation of Lateral Position (SDLP). Testing was conducted after 1 night (a single dose) and after 8 consecutive nights (multiple doses) of treatment with DAYVIGO. Although DAYVIGO at doses of 5 mg and 10 mg 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 10 mg DAYVIGO.

Patients using the 10 mg dose should be cautioned about the potential for next-morning driving impairment because there is individual variation in sensitivity to DAYVIGO (see 7 WARNINGS AND PRECAUTIONS, Driving and Operating Machinery).

Effects on Next-day Postural Stability and Cognitive Performance

The effect of DAYVIGO on next-day postural stability and cognitive performance (tests of attention and

memory) compared to placebo was evaluated in 2 randomized, placebo-controlled clinical studies. DAYVIGO had no significant effects on postural stability compared to placebo. There was no difference from placebo in tests of memory.

Middle of the Night Safety in Older Subjects (age 55 years and older)

The effect of DAYVIGO was evaluated in a randomized, placebo- and active-controlled trial with a scheduled awakening 4 hours after the start of the 8-hour time in bed. Postural stability, the ability to awaken in response to a sound stimulus, and attention and memory were tested following the awakening. Nighttime dosing of DAYVIGO 5 mg and 10 mg 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 up to 105 dB. There were no meaningful differences between DAYVIGO (5 mg or 10 mg) and placebo on ability to awaken to sound.

A computerized performance assessment battery was administered to assess attention and memory after middle of the night awakening (4 hours postdose) in subjects receiving DAYVIGO 5 mg or 10 mg. 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 attention and memory impairment.

10.3 Pharmacokinetics

Absorption

In healthy patients, the pharmacokinetic profile of lemborexant was examined after single doses of up to 200 mg and after once-daily administration of up to 75 mg for 14 days. Lemborexant is rapidly absorbed, with a time to peak concentration (t_{max}) of approximately 1 to 3 hours. Lemborexant exhibits linear pharmacokinetics with multi-exponential decline in plasma concentrations. The extent of accumulation of lemborexant at steady-state is 1.5- to 2-fold across the dose range.

Ingestion of DAYVIGO with a high-fat meal resulted in a slight decrease in the rate of absorption as demonstrated by 23% decrease in lemborexant C_{max} and delay in t_{max} of 2 hours and 18% increase in total exposure AUC. Time to sleep onset may be delayed if taken with or soon after a meal (see 4.1 Dosing Considerations and 9.5 Drug-Food Interactions).

Distribution

In vitro binding of lemborexant and its major circulating metabolite, M10 (the N-oxide of lemborexant) to human plasma proteins ranged from 87.4% to 88.7% and 91.5% to 92.0%, respectively, at concentrations of 100 to 1000 ng/mL. The plasma protein binding is 94% in clinical samples. At these concentrations *in vitro*, lemborexant was bound primarily to human serum albumin, low-density lipoprotein, and high-density lipoprotein. *In vitro* blood to plasma concentration ratios of lemborexant and M10 in humans were 0.610 to 0.656 and 0.562 to 0.616, respectively, at concentrations of 100 to 1000 ng/mL.

Metabolism

Lemborexant metabolism is primarily mediated by CYP3A. M10 is the only major circulating metabolite (12% of parent). The contribution of this metabolite to the pharmacologic activity of lemborexant is

considered minimal.

Elimination

The primary route of elimination is through the feces, with 57.4% of radiolabeled dose recovered in the feces and 29.1% in the urine. The percent of lemborexant excreted unchanged in the urine is negligible (< 1% dose). The effective half-life for lemborexant 5 mg and 10 mg is 17 and 19 hours respectively.

Special Populations and Conditions

- **Pediatrics:** No studies have been conducted to investigate the pharmacokinetics of lemborexant in pediatric patients (see 1.1 Pediatrics; 4.2 Recommended Dose and Dosage Adjustment, Pediatrics and 7.1.3 Pediatrics).
- **Geriatrics:** Based on a population pharmacokinetic analysis of patients receiving 5 or 10 mg DAYVIGO once daily, apparent clearance of lemborexant was 26% lower in elderly patients (> 65 years of age). However, this effect was not clinically relevant (see 1.2 Geriatrics; 4.2 Recommended Dose and Dosage Adjustment, Geriatrics and 7.1.4 Geriatrics).
- **Sex, Body Mass Index (BMI), and Race:** Sex, BMI and race had no clinically meaningful changes on lemborexant pharmacokinetics; therefore, no dose adjustment is required.
- **Hepatic Insufficiency:** Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic insufficiency increased lemborexant AUC and C_{max} by 1.5-fold. Terminal half-life was 1.1 and 1.6 fold longer in subjects with mild and moderate hepatic impairment, respectively. No dose adjustment is recommended for mild hepatic insufficiency; the maximum recommended dose for patients with moderate hepatic insufficiency is 5 mg per day. No data is available for subjects with severe hepatic insufficiency, and lemborexant is not recommended for use in these patients (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Hepatic Impairment and 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).
- **Renal Insufficiency:** Severe renal impairment (urinary creatinine clearance ≤30 mL/min/1.73m^2) increased lemborexant exposure (AUC) 1.5-fold but had no effect on C_{max}. No dose adjustment is required in patients with renal impairment (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Renal Impairment).
- **Breast-feeding:** A milk-only lactation study was conducted in 8 healthy, adult lactating women who received a single 10 mg lemborexant dose showed the presence of lemborexant in human milk. The relative infant dose (RID) was on average 2% of the maternal dose (range 0.8 to 4.5%). The mean amount of lemborexant recovered in human milk was 0.0174 mg following a 10 mg maternal dose. The mean calculated daily infant oral dosage was 0.0029 mg/kg/day based on a nominal infant body weight of 6 kg. Approximately 70% of the total amount of lemborexant excreted in milk was collected by 24 hours after a single maternal dose administration. There are no data on the transfer of lemborexant into breast milk following repeated lemborexant dosing in nursing mothers (see section 7.1.2 Breast-feeding).

11 STORAGE, STABILITY AND DISPOSAL

Store between 15 – 30 °C (room temperature).

Dispense in a container with a child-resistant closure.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

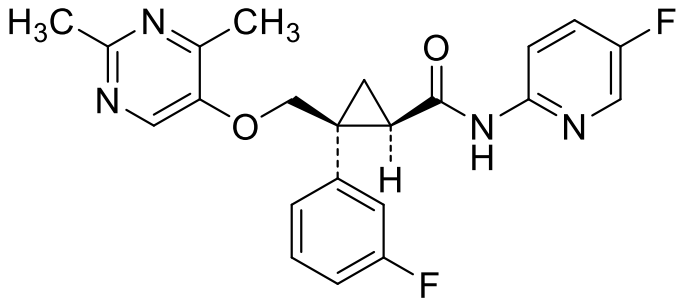
Proper name: lemborexant

Chemical name: (1*R*,2*S*)-2-{[(2,4-dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-N-(5- fluoropyridin-2-yl)cyclopropanecarboxamide

Molecular formula and molecular mass: $C_{22}H_{20}F_2N_4O_2$

410.42

Structural formula:



Physicochemical properties: Lemborexant is a white to off-white powder that is practically insoluble in water.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance

DAYVIGO was evaluated in two clinical trials in patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

Table 5: Summary of patient demographics for clinical trials in insomnia

Study #	***Trial design***	***Dosage, route of administration and duration***	***Study subjects (n=number)***	***Mean age (Range)***	***Sex***
Study 1 (E2006-G000-303)	Phase 3, randomized, double-blind, placebo-controlled, parallel group study	Lemborexant 5 mg, lemborexant 10 mg, or Lemborexant matched placebo was taken orally in tablet form each night, immediately before the time the subject intended to try to	Treatment Phase Total: 959 Lemborexant 5 mg: 319 Lemborexant 10 mg: 319 Placebo: 321	54.5 (18-88)	68.2% Female and 31.8% Male

		sleep. Duration 6-month, placebo-controlled treatment period (Period 1), followed by 6 months of active treatment (Period 2).	Completed: 734		
Study 2 (E2006-G000-304)	Phase 3, randomized, double-blind, placebo- and active-controlled, parallel-group study	All subjects received 2 tablets per day as described below according to the treatment group to which the subject had been randomized: LEM5: 1 lemborexant 5 mg tablet and 1 active-matched placebo LEM10: 1 lemborexant 10 mg tablet and 1 active-matched placebo PBO: 1 lemborexant-matched placebo tablet and 1 active-matched placebo Duration 30 days	Treatment Phase Total: 1006 LEM5: 266 LEM10: 269 Active: 263 Placebo: 208 Completed: 962	63.9 (55-88)	86.4% Female and 13.6% Male

LEM5 = lemborexant 5 mg, LEM10 = lemborexant 10 mg, PBO = placebo

Study 1 was a 6-month, randomized, double-blind, placebo-controlled, multi-center trial in adult patients age 18 or older who met DSM-5 criteria for insomnia disorder. Patients were randomized to placebo (n=325), DAYVIGO 5 mg (n=323), or DAYVIGO 10 mg (n=323) once nightly. The primary efficacy endpoint was the mean change from baseline to end of treatment at 6 months 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 efficacy endpoints for sleep maintenance were change from baseline to end of treatment at 6 months 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. The primary and pre-specified secondary efficacy endpoints were measured by sleep diary.

The demographic characteristics of patients in Study 1 were similar across the treatment arms. Patients had a median age of 55 years (range 18 to 88) and were 68% female, 72% White, 8% Black or African

American, 17% Japanese, and 3.5% other; 28% were elderly (≥65 years).

Study 2 was a 1-month, randomized, double-blind, placebo- and active-controlled, multi-center, parallel-group clinical trial in adult female patients age 55 and older and male patients 65 years and older who met DSM-5 criteria for insomnia disorder. Patients were randomized to placebo (n=208), DAYVIGO 5 mg (n=266) or 10 mg (n=269), or active comparator (n=263) once nightly.

The primary efficacy endpoint 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 in Study 2 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.

The demographic and baseline characteristics of patients in Study 2 were similar across the treatment arms. Patients had a median age of 63 years (range 55 to 88) and were 86% female, 72% White, 25% Black or African American, and 2% other; 45% were elderly (≥65 years).

In Study 1 and Study 2, DAYVIGO 5 mg and 10 mg were superior to placebo for both sleep latency and time spent awake after sleep onset as assessed both subjectively by patient-estimated sleep latency and patient-estimated time spent awake after sleep onset (Table 6) and objectively by polysomnography (Table 7). These effects were sustained through 6 months as assessed subjectively (Table 6).

The efficacy of DAYVIGO was similar between women and men, adult and elderly, and between Caucasians and non-Caucasians.

Table 6: Primary and Secondary Efficacy Results for Change from Baseline in Sleep Diary Assessments of Sleep Parameters Through Month 6 (Study 1)

	Placebo n=318	DAYVIGO 5 mg n=316	DAYVIGO 10 mg n=315	Difference between DAYVIGO and Placebo (95% CI)	
				DAYVIGO 5 mg	DAYVIGO 10 mg
Sleep Onset (sSOL), minutes					
Mean Baseline	63	62	65		
First 7 Nights Mean Change from Baseline	-4	-17	-19	-13*** (-17, -9)	-15*** (-18, -11)
Month 6 Mean Change from Baseline	-17	-29	-32	-12*** (-18, -8)	-15*** (-17, -7)
Sleep Maintenance (sSEF), %					
Mean Baseline	61	63	62		
First 7 Nights LSM Change from Baseline	2	6	8	4*** (2.6, 6.0)	6*** (4.1, 7.5)
Month 6 LSM Change from Baseline	10	14	14	5*** (2.2, 6.9)	5 ** (2.4, 7.0)
Sleep Maintenance (sWASO), minutes					
Mean Baseline	133	133	137		
First 7 Nights LSM Change from Baseline	-5	-19	-21	-14*** (-21, -7)	-17*** (-24, -10)
Month 6 LSM Change from Baseline	-29	-48	-42	-17*** (-27, -8)	-13* (-22, -3)

CI (unadjusted confidence interval); LSM (least squares mean); sSEF (subjective sleep efficiency); sSOL (subjective sleep onset latency); sWASO (subjective wake after sleep onset);
P-values are based on MMRM model with factors for age group, region, treatment, visit (Days 1/2, and Days 29/30), and treatment-by-visit interaction as fixed effects, and the baseline as a covariate. Model for sSOL used log-transformed data.
**P<0.05*
***P <0.01*
****P < 0.001*
Multiplicity adjustment was only applied at Month 6. The comparison of both doses to placebo were statistically significantly superior (p<0.5).

Table 7: Primary and Secondary Efficacy Results for Change from Baseline in Polysomnographic Assessments of Sleep Parameters (Study 2)

	Placebo n=208	DAYVIGO 5 mg n=266	DAYVIGO 10 mg n=269	Difference between DAYVIGO and Placebo (95% CI)	
				DAYVIGO 5 mg	DAYVIGO 10 mg
Sleep Onset (LPS), minutes					
Mean Baseline	44	45	45		
Days 1/2 Mean Change from Baseline	-6	-17	-19	-10** (-14, -6)	-13*** (-17, -9)
Month 1 Mean Change from Baseline	-8	-20	-21	-11*** (-15, -6)	-13*** (-17, -9)

Sleep Maintenance (SEF), %					
Mean Baseline	69	68	68		
Days 1/2 LSM Change from Baseline	5	14	17	9*** (7.7, 10.3)	12*** (10.3, 12.9)
Month 1 LSM Change from Baseline	6	13	14	7*** (5.6, 8.5)	8*** (6.6, 9.5)
Sleep Maintenance (WASO), minutes					
Mean Baseline	112	113	115		
Days 1/2 LSM Change from Baseline	-18	-51	-60	-33*** (-39, -28)	-42*** (-48, -37)
Month 1 LSM Change from Baseline	-21	-45	-47	-24*** (-30, -18)	-25*** (-31, -19)

CI (unadjusted confidence interval); LPS (latency to persistent sleep); LSM (least squares mean); SEF (sleep efficiency); WASO (wake after sleep onset)
P-values are based on MMRM model with factors for age group, region, treatment, visit (Days 1/2, and Days 29/30), and treatment-by-visit interaction as fixed effects, and the baseline as a covariate. Model for LPS used log-transformed data.
**P <0.05*
***P <0.01*
****P <0. 001*
Multiplicity adjustment was done at Month 1 only. The comparison of both doses to placebo were statistically significantly superior (p<0.5).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Single Dose Toxicity

No mortality was observed in single-dose toxicity studies in rats and primates at oral doses up to 1000 mg/kg and systemic exposures 106-217-times and 193-219-times, respectively, the clinical exposure (AUC) at the Maximum Recommended Human Dose (MRHD) (10 mg).

Repeat-Dose Toxicity

In repeat-dose studies in rats, treatment related findings included decreases in body weight gain and food consumption, slight decreases in erythrocytes and hemoglobin, a reactive increase in reticulocytes, and increased total protein and total cholesterol were also observed at higher doses. Increased liver weights and hepatocellular hypertrophy were consistent with microsomal enzyme induction. Adverse changes were observed in bone (histologic structural changes, decreased bone mineral density [BMD], and bone fracture) and teeth (discoloration and histologic changes in ameloblasts) at 100 mg/kg/day and higher in females, and at 1000 mg/kg/day in males. Several investigational studies revealed that these changes were due to fluorosis as a result of animal-specific defluorination of lemborexant during metabolism. Defluorinated metabolites were not identified in humans. No adverse effects were observed in rats at 30 mg/kg/day and exposures 41-times for males and 12-times for females the clinical exposure at the MRHD (10 mg).

In repeat-dose studies in primates, treatment-related vomiting or abnormal stool was observed at doses of 100 mg/kg/day or higher. Slight decreases in erythroid parameters or a reactive increase in reticulocytes were also observed in these groups. Hepatocellular hypertrophy was noted in the liver at doses of 100 mg/kg/day or higher. A minor but dose-dependent increase in urinary fluoride excretion was observed without any adverse changes in the bone. No adverse effects were observed in primates at 10 mg/kg/day and exposures 12-times the clinical exposure at the MRHD (10 mg).

In mice, oral administration of 10 or 30 mg/kg/day resulted in behaviour characteristic of cataplexy when presented with chocolate, a strong emotional stimulus that has been demonstrated to increase cataplexy occurrences in narcoleptic mice.

Carcinogenicity: In a 26-week study in Tg ras H2 mice, there was no evidence of lemborexant-induced neoplasms at oral doses of 50, 150, and 500 mg/kg/day. In a 2-year carcinogenicity study in rats (oral doses of 30, 100, and 300 mg/kg [males] and 10, 30, and 100 mg/kg/day [females]), there was no evidence of lemborexant-induced neoplasms at exposures ≥82 times the exposure at the MRHD based on AUC.

Genotoxicity: Lemborexant was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay. Lemborexant was not clastogenic in the *in vitro* mouse lymphoma thymidine kinase assay or in the *in vivo* rat micronucleus assay.

Reproductive and Developmental Toxicology: In female rats administered lemborexant (oral doses of 30, 100, or 1000 mg/kg/day) prior to and throughout mating and continuing to gestation Day 6, effects on female fertility were observed at doses of 100 and 1000 mg/kg/day (approximately 60 and 545 times the exposure at the MRHD based on AUC). Irregular estrous cycle and decreased pregnancy rate were observed at 100 and 1000 mg/kg/day and decreased numbers of corpora lutea, implantations, and live embryos were noted at 1000 mg/kg/day. The exposure at the NOAEL (30 mg/kg/day) was 12 times the exposure at the MRHD based on AUC. In male rats administered lemborexant (oral doses of 30, 100, or 1000 mg/kg/day) prior to and throughout mating, no effect on male fertility was observed in rats at oral doses up to 1000 mg/kg/day (approximately 138 times the exposure at the MRHD based on AUC).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrDAYVIGO™

Lemborexant Tablets

Read this carefully before you start taking **DAYVIGO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **DAYVIGO**.

What is DAYVIGO used for?

DAYVIGO is used in adults who have trouble falling asleep and/or staying asleep (insomnia).

DAYVIGO is not for use in children under the age of 18 years.

How does DAYVIGO work?

DAYVIGO belongs to a group of medicines called "orexin receptor antagonists". Orexins are substances that bind to certain receptors in your brain to keep you awake. DAYVIGO temporarily blocks these receptors. This may help you fall asleep faster and stay asleep.

What are the ingredients in DAYVIGO?

Medicinal ingredient: lemborexant.

Non-medicinal ingredients: hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose and magnesium stearate. In addition, the film coating contains the following non-medicinal ingredients: hypromellose 2910, polyethylene glycol 8000, talc, titanium dioxide, and

- for the 5 mg tablet: ferric oxide yellow.
- for the 10 mg tablet: ferric oxide red and ferric oxide yellow.

DAYVIGO comes in the following dosage forms:

Film-coated tablet: 5 mg and 10 mg.

Do not use DAYVIGO if:

- you are allergic to lemborexant, or any of the other ingredients of DAYVIGO.
- you have narcolepsy (a sleep disorder that causes excessive daytime sleepiness and causes you to fall asleep often at unexpected times).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DAYVIGO. Talk about any health conditions or problems you may have, including if you:

- have a history of drug or alcohol abuse or addiction.
- have a history of sleeping problems such as falling asleep often at unexpected times (narcolepsy) or feeling sleepy during the day.
- have lung or breathing problems.
- have liver problems.
- are pregnant or plan to become pregnant. It is not known if DAYVIGO can harm your unborn baby. Your healthcare professional will decide whether prescribing DAYVIGO to you outweighs the risk to your unborn baby.
- are breast-feeding or plan to breast-feed. DAYVIGO can pass into your breast milk.
- are lactose intolerant.

Other warnings you should know about:

Check for other existing medical conditions: Sleep problems can be a sign of many physical and mental disorders. Your healthcare professional will need to check your medical history before you start taking DAYVIGO.

Talk to your healthcare professional if after 7 to 10 days of taking DAYVIGO your sleep problems:

- do not stop or do not get better.
- get worse or you develop new abnormal thinking or behaviour.

This may mean that there is another condition such as a physical or mental illness causing your sleep problems.

Abnormal thinking and behavioural changes: When using hypnotics, such as DAYVIGO, you may experience abnormal thinking and changes to your behaviour. These can include:

- memory loss (amnesia) for events that occur when you are not fully awake.
- anxiety.
- seeing or hearing things that are not there (hallucinations) when falling asleep or waking up.

Complex sleep-related behaviours: While taking hypnotic medicines, such as DAYVIGO, you may get out of bed while not being fully awake and do activities that you do not know you are doing, such as:

- sleepwalking.
- driving a car ("sleep-driving").
- eating.
- making phone calls.
- having sex.

The next morning you may not remember what you did during the night. If someone tells you about events you do not remember doing, or you think you may have done things in your sleep you do not

remember doing, stop taking DAYVIGO and **call your healthcare professional**.

You increase your risk of doing activities while not fully awake if you:

- drink alcohol.
- take other medicines that make you feel sleepy.
- have other conditions that affect your sleep that can cause you to wake up often during the night (such as sleep apnea, Periodic Limb Movement Disorder or Restless Leg Syndrome).

Worsening depression and thoughts of suicide: Thoughts of suicide have been reported in people taking DAYVIGO. Some people with depression who took hypnotic medicines saw their depression get worse. They also had increased thoughts of suicide and actions. If you, your caregiver or your family members notice that your depression is getting worse or that you are having thoughts of suicide **call your healthcare professional right away**.

Sleep paralysis, muscle weakness (cataplexy), and hallucinations: You may experience the following when taking DAYVIGO:

- you are not able to move or talk for up to several minutes while you are going to sleep or waking up ("sleep paralysis").
- have sudden muscle weakness, commonly in the legs, that can last a few seconds to a few minutes (cataplexy-like symptoms). This can happen during the day or at night and may not be associated with an identified triggering event (e.g., laughter or surprise).
- seeing or hearing things that are not there (hallucinations) while falling asleep or when you wake up.

If you experience any of these, talk to your healthcare professional.

Driving and using machines: DAYVIGO may affect your ability to be alert the next day.

It may affect how well you drive and you may be at an increased risk of falling asleep while you drive. **Do NOT** drive or use dangerous machinery until you know how taking DAYVIGO affects you the next day.

You can feel less alert:

- even if you take DAYVIGO exactly as prescribed.
- for several days after you stop taking it.

You increase the risk of being less alert the next day if:

- you do NOT get a full night of sleep (**at least** 7 hours).
- take DAYVIGO with other medicines that make you sleepy.
- are taking a higher dose.

If you notice that you are feeling more sleepy or drowsy during the day and it is affecting your ability to do tasks that require clear thinking or attention, talk to your healthcare professional.

Falls: Since DAYVIGO can cause you to feel drowsy, you may be at a higher risk of falls, especially if you are older.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with DAYVIGO:

- alcohol, as it can increase your chances of getting serious side effects. Do NOT drink any alcohol while taking DAYVIGO.
- sedatives (that can make you sleepy). Do NOT take any sedatives or medicines that can make you sleepy. This includes:
    - prescription and over-the-counter sleep products.
    - opioids (used to treat pain).
    - certain antidepressants (used to treat depression).
- itraconazole, ketoconazole and posaconzole (used to treat fungal infections).
- clarithromycin, telithromycin (used to treat bacterial infections).
- bocepravir, telaprevir (used to treat Hepatitis C Virus (HCV)).
- fluconazole (used to treat fungal and yeast infections).
- diltiazem and verapamil (used to treat high blood pressure and chest pain/angina).
- digoxin (used to treat heart failure).
- aprepitant (used to treat nausea and vomiting caused by certain anti-cancer medicines).
- imatinib (used to treat certain types of cancer).
- nefazodone (used to treat depression).
- conivaptan (used to treat low sodium levels).
- rifampin (used to treat bacterial infections).
- carbamazepine and phenytoin (used to treat convulsions and seizures).
- St. John's wort (used to treat depression).
- grapefruit juice.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare professionals each time you get a new medicine.

How to take DAYVIGO:

Take DAYVIGO:

- exactly how and for as long as your healthcare professional has told you to take it.
- once a day at night within a few minutes before going to bed.
- only when you can get a full night of sleep **(at least 7 hours)**.

DAYVIGO may take longer to work if you take it with or soon after eating a meal.

Usual dose:

The recommended daily dose: 5 mg once a day (within a few minutes of going to bed, and with at least 7 hours remaining before you plan to wake up).

The maximum recommended dose: 10 mg once a day (within a few minutes of going to bed and with at least 7 hours remaining before you plan to wake up).

Do NOT take more than 10 mg a day.

Your healthcare professional may change your dose depending on how you respond to DAYVIGO.

Overdose:

If you think you, or a person you are caring for, have taken too much DAYVIGO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose and you do have time to sleep for at least 7 hours before you must wake up again, take your dose as usual.
- If you do not have time to sleep for at least 7 hours before you must wake up again: **Do NOT** take your dose. Take it the next night.

What are possible side effects from using DAYVIGO?

These are not all the possible side effects you may have when taking DAYVIGO. If you experience any side effects not listed here, tell your healthcare professional.

The side effects of DAYVIGO include:

- Sleepiness during the day.
- Headache.
- Nasopharyngitis.
- Fatigue.
- Urinary tract infection.
- Nausea.
- Upper respiratory tract infection.
- Back pain.
- Nightmares.
- Abnormal dreams.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Excessive sleepiness during the day.		✓	
Sleep paralysis: Temporary inability to move or talk for up to several minutes while you are going to sleep or waking up hallucinations or vivid and disturbing perceptions.		✓	
UNCOMMON			
Temporary weakness in the legs that can happen during the day or night		✓	
Abnormal thoughts and behaviour: more outgoing or aggressive behaviour than normal, confusion, agitation, hallucinations, anxiety, memory loss.	✓		
Worsening of depression		✓	
VERY RARE			
Sleepwalking or doing other activities when you are asleep like eating, talking, having sex, or driving a car.			✓
UNKNOWN FREQUENCY			
Thoughts of suicide or actions.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store DAYVIGO:

- at room temperature (15°C - 30°C).
- in the original bottle with the child-resistant closure.
- Do not use this medicine after the expiry date on the bottle.

Keep out of reach and sight of children.

If you want more information about DAYVIGO:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website eisai.ca, or by calling 1-877-873-4724.

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