DAYVIGO Tablets 5mg

Lemborexant Tablets

Caution: DAYVIGO has a habit-forming effect.
Use only pursuant to the prescription or directions of a physician, etc.

CONTRAINDICATIONS

(DAYVIGO is contraindicated in the following patients.)

1. Patients with narcolepsy.
2. Patients with a history of hypersensitivity to the ingredients of this product.
3. Patients with severe hepatic function disorder (plasma lemborexant concentration may increase.) (See the **"PHARMACOKINETICS"** section.)

DESCRIPTION

1. Composition

Each pale-yellow film-coated tablet contains 5 mg of lemborexant. Yellow ferric oxide, titanium oxide, magnesium stearate, talc, low substituted hydroxypropylcellulose, lactose hydrate, hydroxypropylcellulose, hypromellose, and macrogol 6000 are also present as inactive ingredients.

2. Product Description

Brand Name	Formulation Identification Code	Appearance			Descrip-tion
		Top	Bottom	Side	
DAYVIGO Tablets 5mg	film-coated tablets	LEM	5		pale yellow
	LEM 5	Diameter (mm)/Mass (mg)/ Thickness (mm) 7.1/127/3.3			

INDICATION(S)

Insomnia

DOSAGE AND ADMINISTRATION

The usual dosage for adults is 5 mg of lemborexant administered orally once daily immediately before bedtime.

<Precautions regarding dosage and administration>

1. Instruct the patient to take DAYVIGO immediately before bedtime. Instruct the patient not to take DAYVIGO if there is any possibility of waking up temporarily in the middle of sleep to engage in activities, such as to work, after taking this product and going to sleep.
2. Since sleep induction may be delayed, avoid taking DAYVIGO at the same time or right after meals. (With postprandial administration, the plasma lemborexant concentration immediately after the administration may decrease compared to that with administration on an empty stomach.) (See the **"PHARMACOKINETICS"** section.)
3. Concomitant use of DAYVIGO with strong or moderate CYP3A inhibitors is contraindicated. Concomitant use of DAYVIGO with strong or moderate CYP3A inducers is contraindicated. The recommended dosage of DAYVIGO is 5 mg no more than once per night when co-administered with weak CYP3A inhibitors (See the **"PHARMACOKINETICS"** section.)
4. Since plasma lemborexant concentration increase in patients with moderate hepatic function disorder, the dosage may not exceed 5 mg once daily in these patients, and should be administered with care. (See **"Careful Administration"** and the **"PHARMACOKINETICS"** section.)
5. The efficacy and safety of concomitant use with other drugs for treatment of insomnia have not been established.
6. Patients should be advised not to consume alcohol in combination with DAYVIGO.
7. When DAYVIGO is combined with other central nervous system (CNS) depressant drugs, dosage adjustment of DAYVIGO and/or the other drug(s) may be necessary because of potentially additive effects.

PRECAUTIONS

1. Careful Administration (DAYVIGO should be administered with care in the following patients.)

(1) Patients with mild and moderate hepatic function disorder (plasma lemborexant concentration may increase.) (See the **"PHARMACOKINETICS"** section.)
(2) Patients with severe renal impairment (plasma lemborexant concentration may increase.) (See the **"PHARMACOKINETICS"** section.)
(3) Patients with organic brain disorders (effects of DAYVIGO may excessively increase.)
(4) Patients with moderate and severe respiratory function disorder (DAYVIGO has never been administered to these patients, and safety has not been established) (See the **"CLINICAL STUDIES"** section.)

2. Important Precaution(s)

(1) The effects of DAYVIGO may persist until the next morning (or longer) after ingestion, and this product may induce drowsiness as well as impairment of attention, concentration, and reflex movements, so patients should be cautioned against engaging in potentially hazardous activities such as operating machinery or driving a motor vehicle.
(2) When symptoms improve, consider the necessity of continuing DAYVIGO, and take care that DAYVIGO is not aimlessly administered.

3. Drug Interactions

Lemborexant is mainly metabolized by the drug-metabolizing enzyme CYP3A. (See the **"PHARMACOKINETICS"** section.)

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Contraindications for co-administration (Dayvigo should not be co-administered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Strong or moderate CYP3A inhibitors (itraconazole, clarithromy-cin, erythromycin, fluconazole, verapamil, etc.)	These drugs may increase the incidence of adverse reactions. Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inhibitors.	Inhibition of CYP3A, the enzyme metabolizing lemborexant, leads to increased plasma lemborexant concentrations. (see **"PHARMACOKINETICS"** section) Co-administration with strong or moderate CYP3A inhibitors is contraindicated.
Strong or moderate CYP3A inducers (rifampicin, phenytoin, etc.)	These drugs may decrease the effects of DAYVIGO. Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inducers.	Induction of CYP3A, the enzyme metabolizing lemborexant, leads to decreased plasma lemborexant concentrations. Concomitant use of rifampicin with DAYVIGO leads to a decrease in the blood concentration of lemborexant. C_{max} and $AUC_{(0\text{-}inf)}$ of lemborexant were decreased by 92% and 97% compared to those with lemborexant alone, respectively. (See the **"PHARMACOKI-NETICS"** section.)

Considerations when co-administering with other drugs.

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Weak CYP3A inhibitors (chlorzoxazo-ne, rantidine)	These drugs may increase the effects of DAYVIGO.	Inhibition of CYP3A, the enzyme metabolizing lemborexant, leads to increased plasma lemborexant concentrations. (see **"PHARMACOKINETICS"** section) The maximum dosage of DAYVIGO is 5 mg no more than once per night when co-administered with weak CYP3A inhibitors.
CYP2B6 substrates (bupropion, methadone)	Patients receiving DAYVIGO and CYP2B6 substrates concurrently should be monitored for adequate clinical response.	Concomitant use of DAYVIGO decreases the AUC of drugs that are CYP2B6 substrates, which may result in reduced efficacy for these concomitant medications. Increasing the doses of CYP2B6 substrates may be considered as needed.
Central nervous depressants Phenothiazine derivatives Barbiturate derivatives, etc.	DAYVIGO may enhance the depressant effects to central nervous system. These drugs should be administered with care.	DAYVIGO and these drugs have depressant effects to the central nervous system, so may enhance the effects of each other.
Alcohol (drinking)	Since additive decreases in psychomotor functions may occur, instruct the patient to refrain from drinking alcohol while being treated with DAYVIGO.	Concomitant use of alcohol with DAYVIGO leads to increased plasma lemborexant concentrations. Since alcohol has suppressive effects on the central nervous system, an additive effect may occur. (See the **"PHARMACOKI-NETICS"** section.)

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4. Adverse Reaction(s)

Adverse reactions were reported in 249 (28.2%) of the 884 patients (including 155 Japanese patients) who received lemborexant in an international phase III study involving patients with insomnia.

Major adverse reactions included somnolence in 95 patients (10.7%), headache in 37 patients (4.2%), and malaise in 27 patients (3.1%) (as of the time of approval).

(1) Other Adverse Reaction(s)

	≥3%	≥1 and <3%	<1%	Incidence Unknown
Nervous system disorders	Somnolence and headache	Dizziness and sleep paralysis	Disturbance in attention	
Psychiatric disorders		Abnormal dreams and nightmares	Hallucinations, confusional state	
Cardiovascular			Palpitations	
Gastrointestinal		Nausea	Dry mouth and abdominal pain	
Hepatic			ALT (GPT) increased	
Sensory organs			Vertigo and tinnitus	Eye pain Note)
Other	Malaise	Weight increased	Increased appetite, hyperhidrosis, blood triglycerides increased, feeling abnormal, fall, myalgia	

Note) An adverse reaction reported in an overseas clinical study

5. Use in The Elderly

A pharmacokinetic study involving the elderly has revealed a tendency towards increases in plasma concentrations in the elderly compared to those in non-elderly individuals. Given that physiological functions of the elderly are decreased in general, administer DAYVIGO carefully while monitoring the status of the patient. (See the **"PHARMACOKINETICS"** section.)

6. Use during Pregnancy, Delivery or Lactation

(1) Pregnant or possibly pregnant women should receive DAYVIGO only when the benefit of treatment is considered to outweigh the risks. (Safety of use during pregnancy has not been established.)

(2) Avoid treating lactating women with DAYVIGO. When there is no other choice but to administer the drug, instruct them to stop breastfeeding. (Lemborexant and its metabolites reportedly transfer to breast milk in lactating rats.)

7. Pediatric Use

Clinical study in pediatric patients has not been performed.

8. Overdosage

(1) Symptoms and Signs

Little information exists regarding DAYVIGO overdose. A dose-dependent increase in the incidence of somnolence was reported in an overseas clinical study of DAYVIGO administered up to 75 mg to healthy adult subjects.

Hypotonia, photopsia, hypoxia, initial insomnia, coldness, etc. were reported in clinical studies of DAYVIGO administered at >10 mg.

(2) Treatment

Treatment: No specific antidote exists for the treatment of DAYVIGO overdose. Common symptomatic therapy should be provided in the event of overdose.

9. Precautions Concerning Use

At the time of drug delivery:

Instruct the patient to take the drug in the press-through package (PTP) out of the PTP sheet before taking it. Accidental ingestion of a PTP sheet may lead to damage to the esophageal mucous membrane by hard, sharp edges, and furthermore, may cause perforation resulting in serious complications such as mediastinitis.

10. Warning and Precautions

(1) CNS Depressant Effects and Daytime Impairment

DAYVIGO is a CNS depressant that can impair daytime wakefulness even when used as prescribed. CNS depressant effects may persist in some patients for up to several days after discontinuing DAYVIGO. Prescribers should advise patients about the potential for next day somnolence. Driving ability was impaired in some subjects taking DAYVIGO 10 mg. The risk of daytime impairment is increased if DAYVIGO is taken with less than a full night of sleep remaining or if a higher than recommended dose is taken. If DAYVIGO is taken in these circumstances, patients should be cautioned against driving and other activities requiring complete mental alertness. Co-administration with other 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. Patients should be advised not to consume alcohol in combination with

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DAYVIGO because of additive effects. Because DAYVIGO can cause drowsiness, patients, particularly the elderly, are at a higher risk of falls.

(2) 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).

(3) Complex Sleep Behaviors
Complex sleep behaviors, including sleepwalking, sleep-driving, and engaging in other activities while not fully awake (e.g., preparing and eating food, making phone calls, having sex), have been reported to occur with the use of hypnotics such as DAYVIGO. These events can occur in hypnotic naïve as well as in hypnotic-experienced persons. Patients usually do not remember these events. Complex sleep behaviors may occur following the first or any subsequent use of DAYVIGO, with or without the concomitant use of alcohol and other CNS depressants. Discontinue DAYVIGO immediately if a patient experiences a complex sleep behavior.

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

(5) Worsening of Depression/Suicidal Ideation
In clinical studies of DAYVIGO in patients with insomnia, the incidence of suicidal ideation or any suicidal behavior, 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. The emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

(6) 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 behavioral 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.

11. 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.

PHARMACOKINETICS

1. Plasma Concentration
The plasma concentration-time profile after administration of DAYVIGO 10 mg on Day 14 in healthy Japanese adult males who received the drug repeatedly for 14 days at 2.5, 10 or 25 mg once daily are shown in Figure 1. The pharmacokinetic parameters at Day 1 and Day 14 in those who received DAYVIGO 10 mg shown in Table 1. The maximum concentration (C_{max}) and area under the concentration-time curve from 0 to 24 hours ($AUC_{(0-24h)}$) of lemborexant increased with increasing dose. C_{max} was 70.2 ng/mL, and plasma lemborexant concentrations at 3 and 8 hours postdose were 31.4 ng/mL and 17.9 ng/mL, respectively, on Day 14 after administration of 10 mg.[1)]

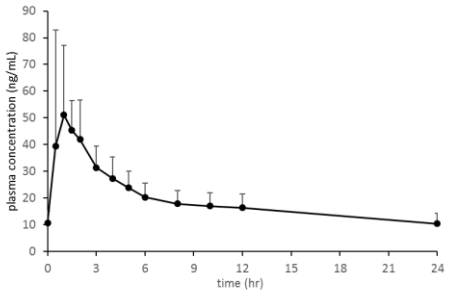


Figure 1 Plasma Concentration-time Profile After Administration of DAYVIGO 10 mg on Day 14 in Healthy Adult (Mean + Standard Deviation)

Table 1 Pharmacokinetic Parameters with Repeated Administration

Dose (mg)	Period of administration	C_{max} (ng/mL)	t_{max} (h)	$AUC_{(0-24h)}$ (ng·h/mL)	$t_{½}$ (h)
10	Day 1	46.5 (25.8)	1.0 (0.5-6.0)	231 (40.2)	-
	Day 14	70.2 (30.2)	1.5 (0.5-2.0)	459 (110)	47.4 (13.9)

All values are shown as mean (standard deviation), except for t_{max}, which is shown as median (minimum value-maximum value).
10 mg: n=6

2. Effects of Meals (Data from Non-Japanese Subjects)

In 24 non-Japanese healthy adults who received DAYVIGO at 10 mg orally as a single dose, the geometric mean ratios (fed/fasted) with 90% confidence intervals (CIs) for C_{max} and $AUC_{(0-t)}$ of lemborexant were 0.771 (0.687, 0.866) and 1.18 (1.09, 1.28), respectively. C_{max} was 23% lower and $AUC_{(0-t)}$ was 18% higher under fed conditions compared with fasted conditions. Furthermore, t_{max} (median) was delayed by 2 hours. The terminal elimination half-life (mean) of lemborexant was 50.8 h under fasted conditions and 53.8 h under fed conditions.[2)] (See the **"Precautions related to dosage and administration"** section.)

3. Distribution

The plasma protein binding (*in vitro* in human plasma) was 87.4-88.7% at concentrations of 100 to 1000 ng/mL.

4. Metabolism

Lemborexant was mainly eliminated from the body through metabolism, with the metabolite with systemic exposure greater than 10% of total drug-related exposure being M10 (N-oxide) alone (13%). M10 was confirmed to contribute to a lesser extent to the pharmacological effects than lemborexant.[4, 5)]

An *in vitro* metabolism study showed that CYP3A is mainly involved in the metabolism of lemborexant. Furthermore, M10 was shown to be generated by oxidative metabolism of lemborexant via CYP3A.[6, 7)]

5. Excretion (Data from Non-Japanese Subjects)

In 8 healthy non-Japanese adult males who received ^{14}C-labelled lemborexant at 10 mg orally as a single dose, the total recovery rate for radioactivity was 86.5%, with 57.4% excreted in feces and 29.1% in urine.

6. Special Population (Data from Non-Japanese Subjects)

(1) Elderly

In 5 healthy elderly subjects (66-76 years) who received DAYVIGO repeatedly for 14 days at 25 mg once daily, geometric mean ratios (healthy elderly/healthy adult) with 90% confidence intervals for C_{max} and $AUC_{(0-24h)}$ of lemborexant on Day 14 were 1.18 [0.770, 1.79] and 1.12 [0.762, 1.64], respectively. C_{max} and $AUC_{(0-24h)}$ were 18% and 12% higher in elderly subjects than in healthy adult subjects, respectively. The terminal elimination half-life (mean) of lemborexant was 49.6 h in healthy adult subjects and 60.1 h in healthy elderly subjects.[9)] In population pharmacokinetic analysis involving healthy adult subjects and patients with insomnia in phase I-III clinical studies, apparent clearance of lemborexant was 26% lower in elderly subjects (≥65 years old).[10)] (See the **"Use in The Elderly"** sections.)

(2) Patients with Hepatic Function Disorder

In 8 patients with mild hepatic function disorder (Child-Pugh score: 5-6) and 8 patients with moderate hepatic function disorder (Child-Pugh score: 7-9) who received DAYVIGO at 10 mg as a single dose, geometric mean ratios (patients with hepatic function disorder/healthy adults) with 90% CIs for C_{max} of lemborexant were 1.58 [1.18, 2.11] and 1.22 [0.915, 1.63], respectively, and those for $AUC_{(0-inf)}$ were 1.25 [0.880, 1.78] and 1.54 [1.06, 2.22], respectively. C_{max} was 58% and 22% higher and $AUC_{(0-inf)}$ was 25% and 54% higher in patients with mild hepatic function disorder and those with moderate hepatic function disorder, respectively, than in healthy adults. The terminal elimination half-lives (mean) of lemborexant were 69.0 h, 78.7 h and 108 h in healthy adult subjects, patients with mild hepatic function disorder and those with moderate hepatic function disorder, respectively. Geometric mean ratios (patients with hepatic function disorder/healthy adults) with 90% CIs for C_{max} of the main metabolite M10 were 0.947 [0.684, 1.31] and 0.766 [0.552, 1.06], respectively, and those for $AUC_{(0-inf)}$ of M10 were 0.950 [0.703, 1.28] and 1.04 [0.754, 1.42], respectively. C_{max} was slightly lower in patients with mild and moderate hepatic function disorder than in healthy adults, but $AUC_{(0-inf)}$ was similar between these patients and healthy adult subjects. The terminal elimination half-lives (mean) of M10 were 64.3 h, 66.6 h and 91.2 h in healthy adults, patients with mild hepatic function disorder and those with moderate hepatic function disorder, respectively. No study of pharmacokinetics has been conducted in patients with severe hepatic function disorder (Child-Pugh score: 10-15).[11)] (See the **"CONTRAINDICATIONS" and "Careful Administration"** section.)

(3) Patients with Renal Impairment

In 8 patients with severe renal impairment (estimated glomerular filtration rate [eGFR] by MDRD equation, 15-29 mL/min/1.73 m^2) who received DAYVIGO at 10 mg as a single dose, geometric mean ratios (patients with renal impairment/healthy adults) with 90% CIs for C_{max} and $AUC_{(0-inf)}$ of lemborexant were 1.05 [0.774, 1.42] and 1.50 [1.13, 1.99], respectively. C_{max} and $AUC_{(0-inf)}$ were 5% and 50% higher in patients with severe renal impairment than in healthy adults, respectively. The terminal elimination half-lives (mean) of lemborexant were 70.0 h and 74.8 h in health adults and

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patients with severe renal impairment, respectively. Geometric mean ratios (patients with renal impairment/healthy adults) with 90% CIs for C_{max} and $AUC_{(0\text{-}inf)}$ of the main metabolite M10 were 0.725 [0.481, 1.09] and 1.36 [0.982, 1.90], respectively. C_{max} was 28% lower and $AUC_{(0\text{-}inf)}$ was 36% higher in patients with severe renal impairment than in healthy adults, respectively. The terminal elimination half-lives (mean) of M10 were 64.0 h and 64.7 h in healthy adults and patients with severe renal impairment, respectively.[12)] (See the **"Careful Administration"** section.)

7. **Drug Interactions (Data from Non-Japanese Subjects)**

(1) Itraconazole

In 15 healthy adults on itraconazole at 200 mg once daily as repeated doses who received DAYVIGO at 10 mg as a single dose, geometric mean ratios (combination therapy/monotherapy) with 90% CIs for C_{max} and $AUC_{(0\text{-}inf)}$ of lemborexant were 1.36 [1.18, 1.57] and 3.70 [3.18, 4.31], respectively. C_{max} and $AUC_{(0\text{-}inf)}$ of lemborexant were 36% and 270% higher with combination therapy than those with monotherapy, respectively. Terminal elimination half-lives (mean) of lemborexant with monotherapy and combination therapy were 54.4 h and 118 h, respectively. Geometric mean ratios (combination therapy/monotherapy) with 90% CIs for C_{max} and $AUC_{(0\text{-}inf)}$ of M10 were 0.130 [0.107, 0.158] and 0.626 [0.465, 0.844], respectively. The terminal elimination half-lives (mean) of M10 with monotherapy and combination therapy were 48.1 h and 150 h, respectively.[13)] (See the **"Precautions related to dosage and administration"** and **"Drug Interactions"** sections.)

(2) Fluconazole

In 14 healthy adults on fluconazole at 200 mg once daily as repeated doses who received DAYVIGO at 10 mg as a single dose, geometric mean ratios (combination therapy/monotherapy) with 90% CIs for C_{max} and $AUC_{(0\text{-}inf)}$ of lemborexant were 1.62 [1.34, 1.97] and 4.17 [3.83, 4.55], respectively. C_{max} and $AUC_{(0\text{-}inf)}$ of lemborexant were 62% and 317% higher with combination therapy than those with monotherapy, respectively. The terminal elimination half-lives (mean) of lemborexant with monotherapy and combination therapy were 55.4 h and 99.5 h, respectively. Geometric mean ratios (combination therapy/monotherapy) with 90% CIs for C_{max} and $AUC_{(0\text{-}inf)}$ of M10 were 0.580 [0.513, 0.657] and 2.33 [1.73, 3.14], respectively. Terminal elimination half-life (mean) of M10 with monotherapy and combination therapy were 45.5 h and 78.6 h, respectively.[14)] (See the **"Precautions related to dosage and administration"** and **"Drug Interactions"** sections.)

(3) Rifampin

In 15 healthy adults on rifampicin at 600 mg once daily as repeated doses who received DAYVIGO at 10 mg as a single dose, geometric mean ratios (combination therapy/monotherapy) with 90% CIs for C_{max} and $AUC_{(0\text{-}inf)}$ of lemborexant were 0.085 [0.067, 0.107] and 0.034 [0.026, 0.045], respectively. C_{max} and $AUC_{(0\text{-}inf)}$ of lemborexant were 92% and 97% lower with combination therapy than those with monotherapy, respectively. The terminal elimination half-lives (mean) of lemborexant with monotherapy and combination therapy were 45.6 h and 10.8 h, respectively. Geometric mean ratios (combination therapy/monotherapy) with 90% CIs for C_{max} and $AUC_{(0\text{-}inf)}$ of M10 were 1.00 [0.884, 1.13] and 0.127 [0.112, 0.145], respectively. The terminal elimination half-lives (mean) of M10 with monotherapy and combination therapy were 39.4 h and 4.07 h, respectively.[13)] (See the "**Drug Interactions"** sections.)

(4) Midazolam

In 28 healthy adults on DAYVIGO at 10 mg once daily as repeated doses who received midazolam at 2 mg as a single dose, geometric mean ratios (combination therapy/monotherapy) with 90% CIs for C_{max} and $AUC_{(0\text{-}inf)}$ of midazolam were 1.13 [1.03, 1.24] and 1.13 [1.02, 1.25], respectively. C_{max} and $AUC_{(0\text{-}inf)}$ of midazolam were 13% and 13% higher with combination therapy than those with monotherapy, respectively. The terminal elimination half-lives (mean) of midazolam with monotherapy and combination therapy were 4.00 h and 4.21 h, respectively.[13)]

(5) Alcohol

In 21 healthy adults on DAYVIGO at 10 mg once daily as a single dose, concomitant intake of alcohol resulted in additive declines in cognition. Moreover, geometric mean ratios (with concomitant intake of alcohol/without concomitant intake of alcohol) with 90% CIs for C_{max} and $AUC_{(0\text{-}72h)}$ of lemborexant were 1.35 [1.14, 1.60] and 1.70 [1.54, 1.89], respectively. C_{max} and $AUC_{(0\text{-}72h)}$ of lemborexant were 35% and 70% higher with concomitant intake of alcohol than without concomitant intake of alcohol, respectively. The terminal elimination half-lives (mean) of lemborexant were 33.9 h and 29.9 h with and without concomitant intake of alcohol, respectively.[15)] (See the "**Drug Interactions"** section.)

Note: The approved dose of DAYVIGO is 5 mg.

CLINICAL STUDIES

1. **Phase III Clinical Study (Study 303)**

Study 303 was a randomized, double-blind, parallel-group study involving patients with insomnia (n=949: Japanese, n=161; adults [18-64 years old], n=687; and elderly [≥65 years old], n=262) consisting of treatment

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period 1 (6 months of treatment with placebo as control) followed by treatment period 2 (6 months of treatment with lemborexant in all subjects). Of the 949, 315 patients were randomized to lemborexant 10 mg, a dose that is not approved for use. Patient-reported, subjective assessments of sleep onset latency, sleep efficiency, and wake after sleep onset using sleep diaries in treatment period 1 are shown in Tables 2, 3 and 4; administrations of DAYVIGO at 5 mg, as compared with placebo, led to statistically significant differences after 6 months of treatment (primary assessment time point).[16)]

Table 2 sSOL (Study 303)

Visits	PBO n=318	LEM5 n=316
BL		
median (min)	55.86	53.57
Change from BL to the first 7 nights		
median (min)	–3.00	–11.00
LSGM ratio*	0.931	0.728
Ratio with PBO**	–	0.781
[95% confidence interval]	–	[0.725, 0.842]
Change from BL to Month 1		
median (min)	–7.14	–13.71
LSGM ratio*	0.786	0.637
LSGM ratio **	–	0.810
[95% confidence interval]	–	[0.735, 0.893]
Change from BL to Month 6		
median (min)	–11.43	–21.81
LSGM ratio*	0.618	0.453
LSGM ratio **	–	0.732
[95% confidence interval]	–	[0.636, 0.843]

* Visit/BL
** Least squares geometric mean ratio: LEM/PBO

Table 3 sSE (Study 303)

Visit	PBO n=318	LEM5 n=316
BL		
mean (%)	61.34	63.14
Change from BL to the first 7 nights		
LSM (%)	2.097	6.396
Difference from PBO * (%)	–	4.299
[95% confidence interval]	–	[2.638, 5.961]
Change from BL to Month 1		
LSM (%)	5.536	7.763
Difference from PBO * (%)	–	2.227
[95% confidence interval]	–	[0.307, 4.146]
Change from BL to Month 6		
LSM (%)	9.640	14.189
Difference from PBO * (%)	–	4.549
[95% confidence interval]	–	[2.236, 6.861]

* LSM difference (LEM–PBO)

Table 4 sWASO (Study 303)

Visits	PBO n=318	LEM5 n=316
BL		
mean (min)	132.49	132.77
Change from BL to the first 7 nights		
LSM (min)	–4.770	–19.098
Difference from PBO * (min)	–	–14.328
[95% confidence interval]	–	[–21.411, –7.245]
Change from BL to Month 1		
LSM (min)	–17.178	–22.692
Difference from PBO * (min)	–	–5.514
[95% confidence interval]	–	[–13.568, 2.540]
Change from BL to Month 6		
LSM (min)	–29.276	–46.750
Difference from PBO * (min)	–	–17.474
[95% confidence interval]	–	[–27.306, –7.643]

* LSM difference (LEM–PBO)

2. Clinical Pharmacology Studies

(1) Effects on Driving Performance (Study 106)

A total of 24 healthy adult male/female subjects (median age, 49 years), including 1 Japanese subject, and 24 healthy elderly male/female subjects (median age, 67 years) received DAYVIGO 5 or 10 mg before bedtime and were evaluated for effects on driving performance the next morning (approximately 9 h after taking the drug). With DAYVIGO administered at 5 or 10 mg over 8 days, no statistically significant effects on driving performance after one or multiple doses were noted in either healthy adult or healthy elderly subjects as compared to placebo.[17)]

(2) Effects on Postural Stability and Cognitive Functions During The Night and The Next Morning (Studies 108 and 304) (Data from Non-Japanese Subjects)

Healthy subjects (≥55 years old) received DAYVIGO 5 or 10 mg before bedtime and were evaluated for the effects on postural stability and cognitive functions (attention and memory) upon awakening during the night (approximately 4 h after administration of DAYVIGO) and upon awakening the next morning (approximately 8 h after administration of DAYVIGO). Approximately 4 h after administration of DAYVIGO, as compared with placebo, increased body sway was noted with DAYVIGO 5 and 10 mg, and decreased attention and memory were noted with DAYVIGO 10 mg. Moreover, in patients with insomnia (≥55 years old) receiving DAYVIGO 5 or 10 mg before bedtime, decreased attention was noted upon awakening the next morning (approximately 8 h after administration) with DAYVIGO 5 and 10 mg, as compared with placebo.[18),19)] There was no effect of DAYVIGO on tests of memory or body sway in the morning.

(3) Respiratory Safety (Study 102) (Data from Non-Japanese Subjects)

In a study of healthy adult and elderly patients, there were no differences between placebo and lemborexant 10 mg and 25 mg with respect to oxygen saturation during sleep. In a study of patients with mild sleep apnea, there was no effect of lemborexant on the apnea-hypopnea index when compared with placebo following single and multiple doses of lemborexant 10 mg. (See the **"Careful Administration"** section.)

(4) Effects on Drug Abuse (Study 103) (Data from Non-Japanese Subjects)

With administration of DAYVIGO at 10, 20 or 30 mg in healthy adults (n=39) with experience of drug abuse, subjective assessments regarding DAYVIGO drug preference and other tendencies toward abuse were higher than those with placebo and similar to those with zolpidem at 30 mg and suvorexant at 40 mg.[21)]

Note: The approved dose of DAYVIGO is 5 mg.

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PHARMACOLOGY

1. Mechanism of Action

In a calcium influx assay, Ki values of lemborexant for human orexin receptor types 1 (OX1) and 2 (OX2) were 8.1 nmol/L and 0.48 nmol/L, respectively.[22] The metabolite M10, which can be found in human plasma, displayed binding affinity at orexin receptors comparable to that of unchanged drug.[23]

Lemborexant is presumed to shift the brain from wakefulness state to sleep state by reversibly blocking the binding of wake-promoting neuropeptides orexin A and orexin B to the receptors OX1 and OX2, thereby inducing sleep.

2. Effects on Sleep

Lemborexant reduced sleep latency and increased total sleep time in rats. No significant difference was noted in the ratio of rapid eye movement (REM) sleep time to total sleep time[24].

PHYSICOCHEMISTRY

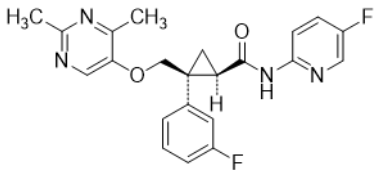
Nonproprietary name: Lemborexant

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 : $C_{22}H_{20}F_2N_4O_2$

Molecular weight : 410.42

Structural formula :



Description : Lemborexant occurs as a white powder and is freely soluble in methanol or benzyl alcohol, soluble in ethanol (99.5), and practically insoluble in water.

Melting point : 177°C

Partition coefficient : 3.7

PACKAGING

DAYVIGO Tablets 5mg : 2 blisters @ 14 film-coated tablets

Storage : Do not store above 30°C.

Expiration Date: Do not use after the expiration date indicated on the outer box or label.

REFERENCES

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2) In-house document: Overseas 008 Study (Approved Jan. 23, 2020, CTD 2.7.6.10)
3) In-house document: The Plasma Protein Binding (*In Vitro*) (Approved Jan. 23, 2020, CTD 2.6.4.4.3)
4) In-house document: Analysis of Metabolites (*In Vivo*) (Approved Jan. 23, 2020, CTD 2.6.4.5.1.2)
5) In-house document: Contribution of Metabolites to Pharmacologic Action (Approved Jan. 23, 2020, CTD 2.6.4.9)
6) In-house document : Identification of CYPs Involved in Metabolism (Approved Jan. 23, 2020, CTD 2.6.4.5.4)
7) In-house document: Putative Metabolic Pathways (Approved Jan. 23, 2020, CTD 2.6.4.5.2)
8) In-house document: A Mass Balance Study (Overseas 007 Study) (Approved Jan. 23, 2020, CTD 2.7.2.2.2.1.3)
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17) Vermeeren, A. et al. : Sleep, **42**, 4（2019. Article Number ZSY260.
18) In-house document: Overseas 108 Study (Approved Jan. 23, 2020, CTD 2.7.6.13)
19) Rosenberg R. et al. : JAMA Network Open, **2**, 12 e 1918254, (2019）
20) In-house document: Overseas 102 Study (Approved Jan. 23, 2020, CTD 2.7.6.6)
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22) In-house document: Calcium Influx Test (Approved Jan. 23, 2020, CTD 2.6.2.2.1.3.2)
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24) Beuckmann, CT. et al. : Sleep, **42**, 6（2019. Article Number ZSZ076.

Reg. No. : XXXXXXXXXXXXXXX

DO NOT DISPENSE WITHOUT PHYSICIAN'S PRE-SCRIPTION (HARUS DENGAN RESEP DOKTER)

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Eisai Manufacturing Limited
UNITED KINGDOM

Imported by:
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