SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DAYVIGO 5 MG film-coated tablet

DAYVIGO 10 MG film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DAYVIGO 5 MG film-coated tablet

Each film-coated tablet contains 5 mg lemborexant.

DAYVIGO 10 MG film-coated tablet

Each film-coated tablet contains 10 mg lemborexant.

For the full list of excipients, see the "List of excipients" section.

3. PHARMACEUTICAL FORM

Film-coated tablet

DAYVIGO 5 MG film-coated tablet

Pale yellow, round, biconvex film-coated tablet, debossed with "LEM" on one side, and "5" on the other side.

DAYVIGO 10 MG film-coated tablet

Orange, round, biconvex film-coated tablet, debossed with "LEM" on one side, and "10" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DAYVIGO is indicated for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance *[see CLINICAL STUDIES]*.

4.2 Posology and method of administration

Posology

Dosing Information

The recommended dosage of DAYVIGO is 5 mg taken no more than once per night, immediately before going to bed, with at least 7 hours remaining before the planned time of awakening. The dose may be increased to the maximum recommended dose of 10 mg based on clinical response and tolerability. Time to sleep onset may be delayed if taken with or soon after a meal *[see PHARMACOLOGICAL PROPERTIES (5)]*.

Dosage Recommendations for Concomitant Use with CYP3A Inhibitors or CYP3A Inducers

Co-administration with Strong or Moderate CYP3A Inhibitors

Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inhibitors *[see Interaction with other medicinal products and other forms of interaction (4.5), PHARMACOLOGICAL PROPERTIES (5)]*.

Co-administration with Weak CYP3A Inhibitors

The maximum recommended dosage of DAYVIGO is 5 mg no more than once per night when co-administered with weak CYP3A inhibitors *[see Interaction with other medicinal products and other forms of interaction (4.5), PHARMACOLOGICAL PROPERTIES (5)]*.

Co-administration with Strong or Moderate CYP3A Inducers

Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inducers *[see Interaction with other medicinal products and other forms of interaction (4.5), PHARMACOLOGICAL PROPERTIES (5)]*.

Dosage Recommendations for Patients with Hepatic Impairment

The maximum recommended dose of DAYVIGO is 5 mg no more than once per night in patients with moderate hepatic impairment *[see Hepatic Impairment, PHARMACOLOGICAL PROPERTIES (5)]*.

DAYVIGO is not recommended in patients with severe hepatic impairment *[see Hepatic Impairment)]*.

Pediatric Use

The safety and effectiveness of DAYVIGO have not been established in pediatric patients.

Geriatric Use

Of the total number of patients treated with DAYVIGO (n=1418) in controlled Phase 3 studies, 491 patients were 65 years and over, and 87 patients were 75 years and over. Overall, efficacy results for patients <65 years of age were similar compared to patients ≥65 years.

In a pooled analysis of Study 1 (the first 30 days) and Study 2, the incidence of somnolence in patients ≥65 years with DAYVIGO 10 mg was higher (9.8%) compared to 7.7% in patients <65 years. The incidence of somnolence with DAYVIGO 5 mg was similar in patients ≥65 years (4.9%) and <65 years (5.1%). The incidence of somnolence in patients treated with placebo was 2% or less regardless of age *[see Clinical Studies (14.2)]*. Because DAYVIGO can increase somnolence and drowsiness, patients, particularly the elderly, are at a higher risk of falls *[see Warnings and Precautions (5.1)]*. Exercise caution when using doses higher than 5 mg in patients ≥65 years old.

Renal Impairment

No dose adjustment is required in patients with mild, moderate, or severe renal impairment.

DAYVIGO exposure (AUC) was increased in patients with severe renal impairment. Patients with severe renal impairment may experience an increased risk of somnolence *[see PHARMACOLOGICAL PROPERTIES (5)]*.

Hepatic Impairment

DAYVIGO has not been studied in patients with severe hepatic impairment. Use in this population is not recommended *[see Dosage Recommendations for Patients with Hepatic Impairment, PHARMACOLOGICAL PROPERTIES (5)]*.

DAYVIGO exposure (AUC and C_{max}) and terminal half-life were increased in patients with moderate hepatic impairment (Child-Pugh class B). Dosage adjustment is recommended in patients with moderate hepatic impairment (Child-Pugh class B) *[see Dosage Recommendations for Patients with Hepatic Impairment, PHARMACOLOGICAL PROPERTIES (5)]*.

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 PHARMACOLOGICAL PROPERTIES (5)]*.

Patients with Compromised Respiratory Function

In a study of patients with mild OSA (apnea-hypopnea index <15 events per hour of sleep), DAYVIGO did not increase the frequency of apneic events or cause oxygen desaturation.

DAYVIGO has not been studied in patients with COPD or moderate to severe OSA. Clinically meaningful respiratory effects of DAYVIGO in COPD or moderate to severe OSA cannot be excluded *[see Special warnings and precautions for use (4.4)]*.

Method of administration

For oral use.

4.3 Contraindications

DAYVIGO is contraindicated in patients with narcolepsy.

4.4 Special warnings and precautions for use

CNS Depressant Effects and Daytime Impairment

DAYVIGO is a central nervous system (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 *[see CLINICAL STUDIES]*. 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 Posology and method of administration (4.2)]*. 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 DAYVIGO

because of additive effects *[see Interaction with other medicinal products and other forms of interaction (4.5)]*.

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

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).

Complex Sleep Behaviors

Complex sleep behaviors, including sleep-walking, 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 *[see Interaction with other medicinal products and other forms of interaction (4.5)]*. Discontinue DAYVIGO immediately if a patient experiences a complex sleep behavior.

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) *[see Patients with Compromised Respiratory Function]*.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs Having Clinically Important Interactions with DAYVIGO

Table 1: Clinically Important Drug Interactions with DAYVIGO

Effect of Other Drugs on DAYVIGO	
Strong, Moderate, and Weak CYP3A Inhibitors	
Clinical Impact:	Concomitant use with a strong, moderate, or weak CYP3A inhibitor increases lemborexant AUC and C_{max} which may increase the risk of DAYVIGO adverse reactions *[see PHARMACOLOGICAL PROPERTIES (5)]*.
Intervention:	Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inhibitors *[see Dosage and Administration (2.2)]*. The maximum recommended dose of DAYVIGO with weak CYP3A inhibitors is 5 mg *[see Posology and method of administration (4.2)]*.
Examples:	Strong CYP3A inhibitors: itraconazole, clarithromycin Moderate CYP3A inhibitors: fluconazole, verapamil Weak CYP3A inhibitors: chlorzoxazone, ranitidine
Strong and Moderate CYP3A Inducers	
Clinical Impact:	Concomitant use with a strong or moderate CYP3A inducer decreases lemborexant exposure, which may reduce DAYVIGO efficacy *[see PHARMACOLOGICAL PROPERTIES (5)]*.
Intervention:	Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inducers *[see Posology and method of administration (4.2)]*.
Examples:	Strong CYP3A inducers: rifampin, carbamazepine, St. John's wort Moderate CYP3A inducers: bosentan, efavirenz, etravirine, modafinil
Alcohol	

Clinical Impact:	Concomitant use of alcohol increases lemborexant C_{max} and AUC. Co-administration of DAYVIGO with alcohol produced a numerically greater negative impact on postural stability and memory as compared with alcohol alone when assessed near the t_{max} of DAYVIGO (2 hours post-dose) *[see PHARMACOLOGICAL PROPERTIES (5)]*.
Intervention:	Avoid alcohol consumption with DAYVIGO *[see Special warnings and precautions for use (4.4)]*.
Effect of DAYVIGO on Other Drugs	
CYP2B6 Substrates	
Clinical Impact:	Concomitant use of DAYVIGO decreases the AUC of drugs that are CYP2B6 substrates, which may result in reduced efficacy for these concomitant medications *[see PHARMACOLOGICAL PROPERTIES (5)]*.
Intervention:	Patients receiving DAYVIGO and CYP2B6 substrates concurrently should be monitored for adequate clinical response. Increasing the doses of CYP2B6 substrates may be considered as needed.
Examples:	Bupropion, methadone

4.6 Fertility, pregnancy and lactation

1 Pregnancy

Risk Summary

There are no available data on DAYVIGO use in pregnant women to evaluate for drug-associated risks of major birth defects, miscarriage or adverse maternal or fetal outcomes.

In animal reproduction studies, oral administration of lemborexant to pregnant rats and rabbits during the period of organogenesis caused toxicities only at high multiples of the human exposure at the maximum recommended human dose (MRHD) based on AUC. The no observed adverse effect levels (NOAEL) are approximately >100 and 23 times the MRHD based on AUC in rats and rabbits, respectively. Similarly, oral administration of lemborexant to pregnant and lactating rats caused toxicities only at high multiples of the human exposure at the MRHD based on AUC. The NOAEL is 93 times the MRHD based on AUC *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Lemborexant was administered orally to pregnant rats during the period of organogenesis in 2 studies at doses of 60, 200, and 600 mg/kg/day or 20, 60, and 200 mg/kg/day, which are approximately 6 to >300 times the MRHD based on AUC. Lemborexant caused maternal toxicity, manifested by decreased body

weight and food consumption, decreased mean fetal body weight, an increased number of dead fetuses, and skeletal, external and visceral malformations (omphalocele, cleft palate, and membranous ventricular septal defect) at >300 times the MRHD based on AUC. The NOAEL of 200 mg/kg/day is approximately 143 times the MRHD based on AUC.

Lemborexant was administered orally to pregnant rabbits during the period of organogenesis at doses of 10, 30, and 100 mg/kg/day, which are approximately 7 to 139 times the MRHD based on AUC. Lemborexant caused maternal toxicity that consisted of decreased body weight and food consumption and a higher incidence of skeletal variations (presence of cervical ribs and supernumerary lung lobes) at approximately 139 times the MRHD based on AUC. The NOAEL of 30 mg/kg/day is approximately 23 times the MRHD based on AUC.

Lemborexant was administered orally to pregnant rats during pregnancy and lactation at doses of 30, 100, and 300 mg/kg/day, which are approximately 15 to 206 times the MRHD based on AUC. Lemborexant caused maternal toxicity that consisted of decreased body weight and food consumption and toxicity to offspring consisting of decreased pup body weights, decreased femur length, and decreased acoustic startle responses at 206 times the MRHD based on AUC. The NOAEL of 100 mg/kg/day is approximately 93 times the MRHD based on AUC.

2 Lactation

Risk Summary

There are no data on the presence of lemborexant in human milk, the effects on the breastfed infant, or the effects on milk production. Lemborexant and its metabolites are present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Infants exposed to DAYVIGO through breastmilk should be monitored for excessive sedation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DAYVIGO and any potential adverse effects on the breastfed infant from DAYVIGO or from the underlying maternal condition.

4.7 Effects on ability to drive and use machines

Although lemborexant 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 lemborexant. 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 lemborexant *[see Special Safety Studies]*.

4.8 Undesirable effects

Summary of the safety profile

The safety of DAYVIGO was evaluated in 1418 adult patients with insomnia disorder (age 18 to 88 years) from two controlled efficacy trials (Study 1 and Study 2). Study 1 was a 6-month placebo controlled trial assessing DAYVIGO 5 or 10 mg once nightly, followed by a 6-month parallel-group extension period in which patients initially treated with DAYVIGO continued on the same dose, and patients who received placebo were re-randomized to receive DAYVIGO 5 or 10 mg once nightly. In Study 1, 434 patients were treated with DAYVIGO for one year. Study 2 was a 30-day placebo- and active-controlled trial assessing DAYVIGO 5 or 10 mg once nightly.

Adverse Reactions Resulting in Discontinuation of Treatment

The frequencies of discontinuation due to adverse reactions in Study 1 (the first 30 days) and Study 2 were 2.6% and 1.4% for patients treated with 10 mg and 5 mg DAYVIGO, respectively, compared to 1.5% for patients in the placebo group. The most common adverse reactions leading to discontinuation of DAYVIGO were somnolence (1.0% for 10 mg, 0.7% for 5 mg, and 0.4% for placebo) and nightmares (0.3% for 10 mg, 0.3% for 5 mg, and 0% for placebo). The frequencies of discontinuation due to adverse reactions in the 6-month placebo-controlled period of Study 1 were 8.3% and 4.1% for patients treated with DAYVIGO 10 mg and 5 mg, respectively, compared to 3.8% for patients in the placebo group. The most common reasons for discontinuation of DAYVIGO and occurring in more than one patient within a treatment arm were somnolence (2.9% for 10 mg, 1.0% for 5 mg, and 0.6% for placebo), nightmares (1.3% for 10 mg, 0.3% for 5 mg, and 0% for placebo), and palpitations (0.6% for 10 mg, 0% for 5 mg, and 0% for placebo).

Most Common Adverse Reactions

The most common adverse reaction (reported in 5% or more of patients treated with DAYVIGO and at least twice the rate of placebo) in Study 1 (the first 30 days) and Study 2 was somnolence (10% for DAYVIGO 10 mg, 7% for DAYVIGO 5 mg, and 1% for placebo).

Tabulated list of adverse reactions

In the table below, adverse reactions, which were Reported in ≥2% of DAYVIGO-Treated Patients and at a Greater Frequency than Placebo-Treated Patients During the First 30 Days of Study 1 and Study 2, are listed by System Organ Class and frequency. The following convention has been used for the classification of adverse reactions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), not known (cannot be estimated from the available data).

Within each frequency category, adverse reactions are presented in order of decreasing seriousness

System Organ Class	Very Common	Common	Uncommon	Not known
Nervous system disorders		Somnolence or fatigue* Headache Sleep paralysis		
Psychiatric disorders		Abnormal dreams or Nightmare	Hypnagogic hallucination Complex sleep behavior	

*Combines preferred terms somnolence, lethargy, fatigue, sluggishness

4.9 Overdose

There is limited clinical experience with DAYVIGO overdose. In clinical pharmacology studies, healthy patients who were administered multiple doses of up to 75 mg (7.5 times the maximum recommended dose) of DAYVIGO showed dose-dependent increases in the frequency of somnolence.

There is no available specific antidote to an overdose of DAYVIGO. In the event of overdose, standard medical practice for the management of any overdose should be used.

The value of dialysis in the treatment of overdosage has not been determined with lemborexant. As lemborexant is highly protein-bound, hemodialysis is not expected to contribute to elimination of lemborexant.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

1 Mechanism of Action

The mechanism of action of lemborexant in the treatment of insomnia is presumed to be through antagonism of orexin receptors. The orexin neuropeptide signaling system plays a role in wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress wake drive.

2 Pharmacodynamics

Lemborexant binds to orexin receptors OX1R and OX2R and acts as a competitive antagonist (IC_{50} values of 6.1 nM and 2.6 nM, respectively). A major metabolite of lemborexant, M10, binds with comparable affinity as the parent drug to orexin receptors OX1R and OX2R (IC_{50} values of 4.2 nM and 2.9 nM), respectively.

Cardiac Electrophysiology

In a concentration-QTcF analysis using the data from two randomized, double-blind, placebo-controlled, multiple ascending dose studies in healthy subjects, lemborexant does not prolong the QTcF interval to any clinically relevant extent at a dose 5 times the maximum recommended dose.

Drug Interactions

Lemborexant co-administered with alcohol produced a numerically greater negative impact on postural stability and memory as compared with alcohol alone at approximately 2 hours post-dose *[see Interaction with other medicinal products and other forms of interaction (4.5)]*.

3 Pharmacokinetics

Following single doses of lemborexant 2.5 to 75 mg, geometric mean C_{max} and AUC_{0-24h} increased slightly less than in proportion to dose. The extent of accumulation of lemborexant at steady-state is 1.5- to 3-fold across this dose range.

Absorption

The time to peak concentration (t_{max}) of lemborexant is approximately 1 to 3 hours.

Effect of Food

Lemborexant C_{max} decreased by 23%, AUC_{0-inf} increased by 18%, and t_{max} was delayed by 2 hours following administration of a high-fat and high-calorie meal (containing approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively).

Distribution

The volume of distribution of lemborexant is 1970 L. Protein binding of lemborexant is approximately 94% *in vitro*. The blood to plasma concentration ratio of lemborexant is 0.65.

Elimination

Metabolism

Lemborexant is primarily metabolized by CYP3A4, and to a lesser extent by CYP3A5. The major circulating metabolite is M10.

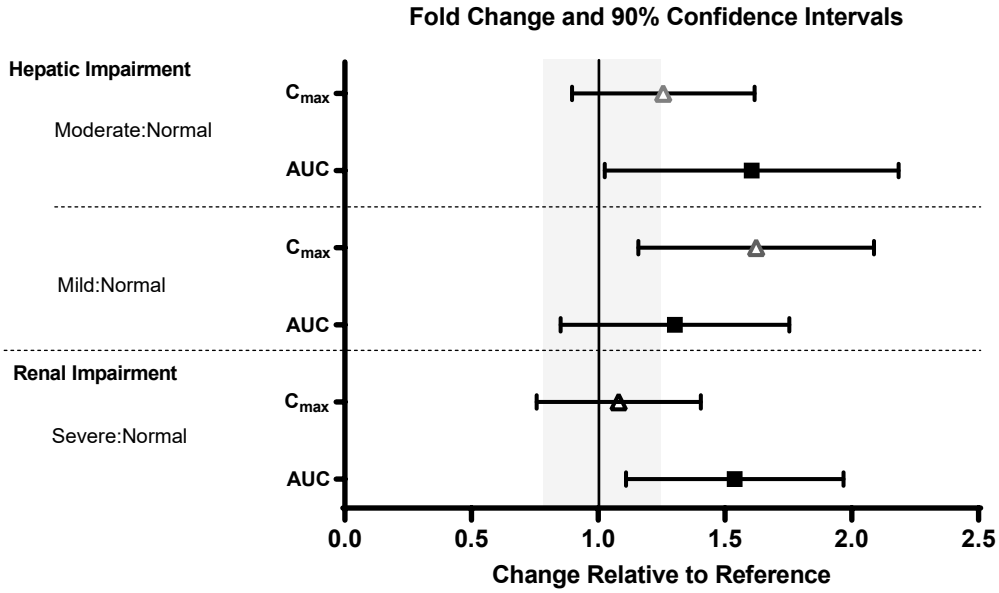
Excretion

Following administration of an oral dose, 57.4% of the dose was recovered in the feces and 29.1% in the urine (<1% as unchanged). The effective half-life for lemborexant 5 mg and 10 mg is 17 and 19 hours, respectively.

Specific Populations

No clinically significant differences in the pharmacokinetics of lemborexant were observed based on age, sex, race/ethnicity, or body mass index. No studies have been conducted to investigate the pharmacokinetics of lemborexant in pediatric patients. Exposures of lemborexant in patients with hepatic and renal impairment are summarized in Figure 1.

Figure 1. Effects of Hepatic and Renal Impairment on Lemborexant Pharmacokinetics



Drug Interaction Studies

The effects of other drugs on the exposures of lemborexant are summarized in Figure 2. The effects of lemborexant on the exposures of other drugs are summarized in Figure 3.

Physiologically-based pharmacokinetic (PBPK) modeling predicted that concomitant use of weak CYP3A inhibitors increased lemborexant exposure by less than 2-fold. Based on these results, drug interactions between lemborexant and strong CYP3A inducers, strong CYP3A inhibitors, moderate CYP3A inhibitors, and CYP2B6 substrates are clinically significant.

Figure 2. Effects of Co-administered Drugs on the Pharmacokinetics of Lemborexant 10 mg

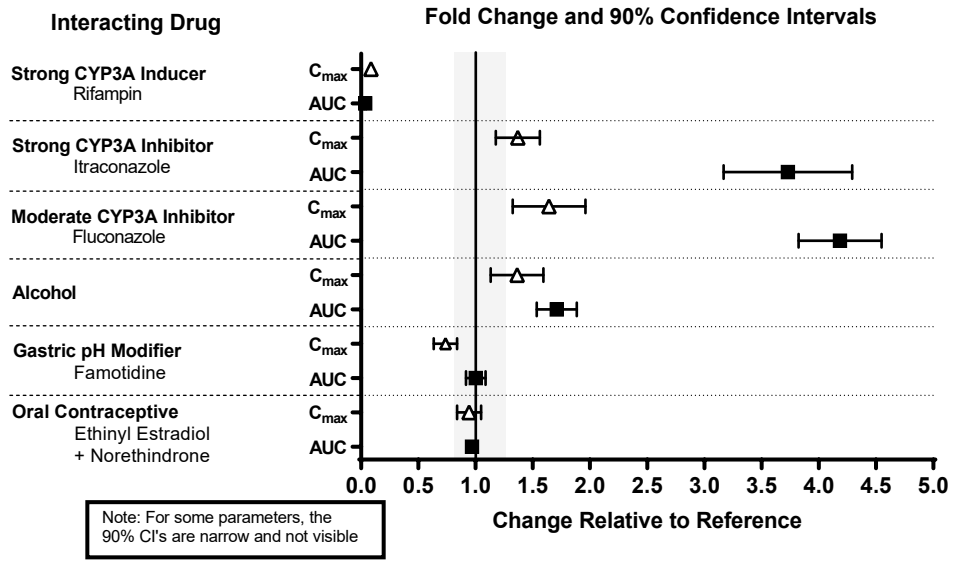
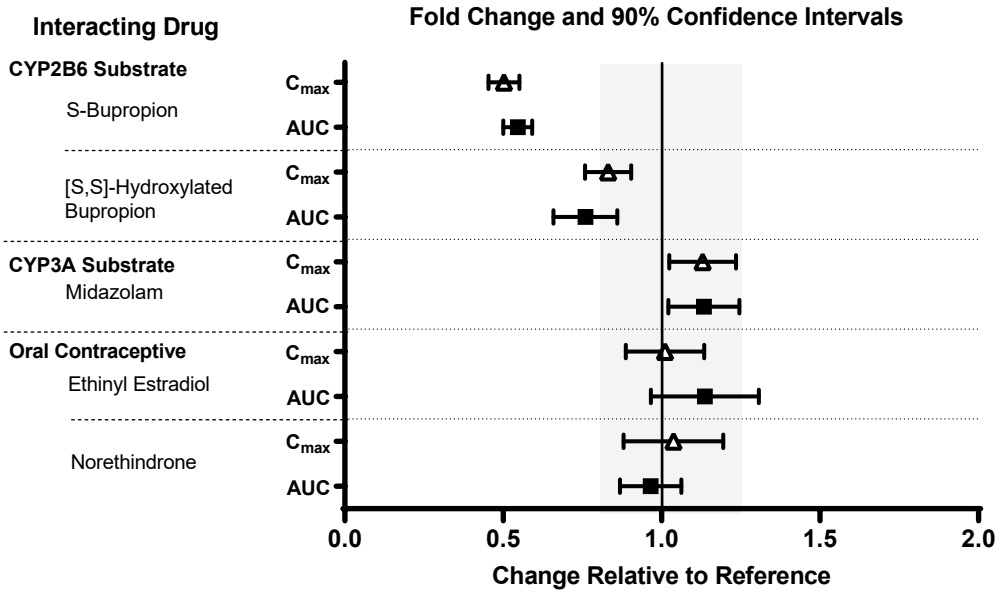


Figure 3. Effects of Lemborexant 10 mg on the Pharmacokinetics of Co-Administered Drugs



In Vitro Studies

In vitro metabolism studies demonstrated that lemborexant and M10 have the potential to induce CYP3A and the weak potential to inhibit CYP3A and induce CYP2B6. Lemborexant and M10 do not inhibit other CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2A6, CYP2C19, and CYP2E1) or transporters (P-gp, BCRP, BSEP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1, and MATE2-K). Lemborexant is a potential poor substrate of P-gp, but M10 is a substrate of P-gp. Lemborexant and M10 are not substrates of BCRP, OATP1B1, or OATP1B3.

CLINICAL STUDIES

1 Controlled Clinical Studies

DAYVIGO was evaluated in two clinical trials in patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance (Study 1, NCT02952820 and Study 2, NCT02783729).

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).

Examination of subgroups by age, race, and sex did not suggest differences in response to DAYVIGO. In Study 1, DAYVIGO 5 mg and 10 mg demonstrated statistically significant superiority on the primary efficacy measure, sSOL, compared to placebo (Table 2). DAYVIGO 5 mg and 10 mg also showed statistically significant superiority in sSEF and sWASO.

Table 3: Primary and Secondary Efficacy Results for Change from Baseline in Sleep Onset and Sleep Maintenance at 6 Months in Patients with Insomnia (Study 1)

Endpoint	Treatment Group	Number of Patients ITT	Baseline Mean[a] (SD)	Month 6 LS Mean[a] (SE)	Treatment Effect (95% CI)
Sleep Onset sSOL (minutes)	DAYVIGO 5 mg*	316	43.0 (31.5)	20.0 (1.1)	0.7 (0.6, 0.8)
	DAYVIGO 10 mg*	315	45.0 (33.4)	19.2 (1.1)	0.7 (0.6, 0.8)
	Placebo	318	45.0 (31.8)	27.3 (1.4)	(ratio vs placebo)[b]
Sleep Maintenance sSEF (%)	DAYVIGO 5 mg*	316	63.1 (18.2)	75.9 (0.9)	4.5 (2.2, 6.9)
	DAYVIGO 10 mg*	315	62.0 (17.2)	75.9 (0.9)	4.7 (2.4, 7.0)
	Placebo	318	61.3 (17.8)	71.4 (0.8)	(%)[c]
Sleep Maintenance sWASO (minutes)	DAYVIGO 5 mg*	316	132.8 (82.5)	87.9 (3.7)	-17.5 (-27.3, -7.6)
	DAYVIGO 10 mg*	315	136.8 (87.4)	92.7 (3.7)	-12.7 (-22.4, -3.0)
	Placebo	318	132.5 (80.2)	105.3 (3.6)	(minutes)[c]

ITT (intention to treat); sSOL (subjective sleep onset latency); SD (standard deviation); LS (least squares); SE (standard error); CI (unadjusted confidence interval); sSEF (subjective sleep efficiency); sWASO (subjective wake after sleep onset)

[a] For the sleep onset sSOL endpoint, the mean refers to geometric mean, which was used due to the approximately log normal distribution of the outcomes; SD for the geometric mean is calculated as GM*SD (log transformed sSOL); SE for the least squares geometric mean is calculated in the same way as the SD.

[b] For the sleep onset sSOL endpoint, treatment effect refers to the ratio of [Month 6 sSOL / Baseline sSOL] for DAYVIGO versus placebo, such that a smaller ratio corresponds to a greater improvement.

[c] Treatment effect refers to the treatment difference between DAYVIGO versus placebo, such that a larger value for sSEF and smaller value for sWASO correspond to greater improvement.

* Doses that were statistically significantly superior ($p<0.05$) to placebo after multiplicity adjustment.

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 2, DAYVIGO 5 mg and 10 mg demonstrated statistically significant superiority on the primary efficacy measure, LPS, compared to placebo (Table 4). DAYVIGO 5 mg and 10 mg demonstrated statistically significant improvement in SEF and WASO compared to placebo.

Table 4: Primary and Secondary Efficacy Results for Change from Baseline in Sleep Onset and Sleep Maintenance at 1 Month in Patients with Insomnia (Study 2)

Endpoint	Treatment Group	Number of Patients ITT	Baseline Mean[a] (SD)	Day 29/30 LS Mean[a] (SE)	Treatment Effect (95% CI)
Sleep Onset LPS (minutes)	DAYVIGO 5 mg*	266	33.0 (27.2)	15.5 (0.8)	0.8 (0.7, 0.9)
	DAYVIGO 10 mg*	269	33.3 (27.2)	14.5 (0.7)	0.7 (0.6, 0.8)
	Placebo	208	33.6 (25.9)	20.0 (1.1)	(ratio vs. placebo)[b]
Sleep Maintenance SEF (%)	DAYVIGO 5 mg*	266	68.4 (11.3)	80.7 (0.5)	7.1 (5.6, 8.5)
	DAYVIGO 10 mg*	269	67.8 (10.8)	82.7 (0.5)	8.0 (6.6, 9.5)
	Placebo	208	68.9 (9.6)	74.6 (0.6)	(%)[c]
Sleep Maintenance WASO (minutes)	DAYVIGO 5 mg*	266	113.4 (39.0)	68.3 (2.2)	-24.0 (-30.0, -18.0)
	DAYVIGO 10 mg*	269	114.8 (40.0)	66.9 (2.2)	-25.3 (-31.4, -19.3)
	Placebo	208	111.7 (37.2)	92.2 (2.5)	(minutes)[c]

ITT (intention to treat); LPS (latency to persistent sleep); SD (standard deviation); LS (least squares); SE (standard error); CI (unadjusted confidence interval); SEF (sleep efficiency); WASO (wake after sleep onset)

[a] For the sleep onset LPS endpoint, the mean refers to geometric mean, which was used due to the approximately log normal distribution of the outcomes; SD for the geometric mean is calculated as GM*SD (log transformed LPS); SE for the least squares geometric mean is calculated in the same way as the SD.

[b] For the LPS endpoint, treatment effect refers to the ratio of [Day 29/30 LPS / Baseline LPS] for DAYVIGO versus placebo, such that a smaller ratio corresponds to a greater improvement.

[c] Treatment effect refers to the treatment difference between DAYVIGO versus placebo, such that a larger value for SEF and smaller value for WASO correspond to greater improvement.

* Doses that were statistically significantly superior ($p<0.05$) to placebo after multiplicity adjustment.

The effects of DAYVIGO at the beginning of treatment were generally consistent with later timepoints.

2 Special Safety Studies

Middle of the Night Safety

The effect of DAYVIGO on middle of the night safety was evaluated in a randomized, placebo- and active-controlled trial in healthy female subjects ≥55 years or male subjects ≥65 years. Postural stability, the ability to awaken in response to a sound stimulus, and attention and memory were assessed following a scheduled awakening 4 hours after the start of the 8-hour time in bed. Postural stability was measured by assessing body sway using an ataxia meter. Nighttime dosing of DAYVIGO 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.

Effects on Next-day Postural Stability and Memory

The effects of DAYVIGO on next day postural stability and memory were evaluated in two randomized, placebo- and active-controlled trials in healthy subjects and insomnia patients age 55 and older.

There were no meaningful differences between DAYVIGO (5 mg or 10 mg) and placebo on next-day postural stability or memory compared to placebo.

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 subjects (≥65 years, median age 67 years; 14 men, 10 women) and 24 adult subjects (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 one night (a single dose) and after eight consecutive nights 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.

Rebound Insomnia

Rebound insomnia was assessed by comparing sleep diary-recorded sSOL and sWASO from the screening period to the two weeks following treatment discontinuation in both Studies 1 and 2. Analyses

of group means and the proportion of patients with rebound insomnia suggest that DAYVIGO was not associated with rebound insomnia following treatment discontinuation.

Withdrawal Effects

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

5.3 Preclinical safety data

1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lemborexant did not increase the incidence of tumors in rats treated for 2 years at oral doses of 30, 100, and 300 mg/kg/day (males) and 10, 30, and 100 mg/kg/day (females), which are >80 times the MRHD based on AUC. Lemborexant did not increase the incidence of tumors in Tg ras H2 mice treated for 26 weeks at oral doses of 50, 150, and 500 mg/kg/day.

Mutagenesis

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

Impairment of Fertility

Lemborexant was orally administered to female rats at doses of 30, 100, or 1000 mg/kg/day prior to and throughout mating and continuing to gestation Day 6. These doses are approximately 12 to >500 times the MRHD based on AUC. Irregular estrous cycles and decreased pregnancy rate were observed at 60 times the MRHD based on AUC, and decreased numbers of corpora lutea, implantations, and live embryos were observed at >500 times the MRHD based on AUC. The exposure at the NOAEL of 30 mg/kg/day is approximately 12 times the MRHD based on AUC. Lemborexant did not affect fertility when orally administered to male rats at doses of 30, 100, or 1000 mg/kg/day prior to and throughout mating; the highest dose is approximately 138 times the MRHD based on AUC.

2 Animal Toxicology and/or Pharmacology

Lemborexant administered to mice at oral doses of 10 or 30 mg/kg resulted in behavior characteristic of cataplexy when presented with chocolate. Chocolate is a stimulus that has been demonstrated to increase cataplexy occurrences in narcoleptic mice.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients

5 mg tablets: 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.

10 mg tablets: Each orange film-coated tablet contains 10 mg of lemborexant. Yellow ferric oxide, titanium oxide, red ferric oxide, magnesium stearate, talc, low substituted hydroxypropylcellulose, lactose hydrate, hydroxypropylcellulose, hypromellose, and macrogol 6000 are also present as inactive ingredients.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Storage: Do not store above 30°C.

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

6.5 Nature and contents of container

Polyvinyl chloride (PVC) film/aluminum foil blister sheets.

6.6 Special precautions for disposal

No special requirements.

7. MANUFACTURED BY:

Eisai Manufacturing Limited

European Knowledge Centre, Mosquito Way, Hatfield, AL10 9SN, United Kingdom

8. IMPORTED BY:

Eisai (Thailand) Marketing Co., Ltd.

Bangkok, Thailand

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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