SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

DAYVIGO 5, Film-coated tablets

DAYVIGO 10, Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DAYVIGO 5

Each film-coated tablet contains lemborexant 5 mg.

DAYVIGO 10

Each film-coated tablet contains lemborexant 10 mg.

Excipient(s) with known effect:

DAYVIGO 5 contains 93,88 mg lactose monohydrate per tablet.

DAYVIGO 10 contains 88,88 mg lactose monohydrate per tablet.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

DAYVIGO 5: Pale yellow, round, biconvex film-coated tablets debossed “LЄM” on one side and “5” on the other side.

DAYVIGO 10: Orange, round, biconvex film-coated tablets debossed “LЄM” 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.

4.2 Posology and method of administration

Posology

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.

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 section 4.5).

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 section 4.5).

Co-administration with Strong or Moderate CYP3A Inducers

Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inducers (see section 4.5).

Special populations

Hepatic impairment

The maximum recommended dose of DAYVIGO is 5 mg no more than once per night in patients with moderate (Child-Pugh class B) hepatic impairment (see section 5.2 Pharmacokinetic properties, Special populations). DAYVIGO is not recommended in patients with severe hepatic impairment (see section 4.4)

Renal Impairment

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

Elderly

Elderly (≥ 65 years of age): No clinically meaningful differences in safety or effectiveness were observed between elderly patients ≥ 65 years of age and younger patients at the recommended doses. No dose adjustment is required in elderly patients

Patients with compromised respiratory function

Effects of DAYVIGO on respiratory function should be considered if prescribed to patients with compromised respiratory function. In a study of patients with mild obstructive sleep apnoea (apnoea-hypopnoea index >5 and <15 events per hour of sleep), DAYVIGO did not increase the frequency of apnoeic events or cause oxygen desaturation. DAYVIGO has not been studied in patients with chronic obstructive pulmonary disease or moderate to severe obstructive sleep apnoea (OSA).

Paediatric population

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

Method of administration

DAYVIGO tablets are intended for oral administration.

Time to sleep onset may be delayed if taken with or soon after a meal.

4.3 Contraindications

- Hypersensitivity to lemborexant or to any of the excipients (see section 6.1)
- 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. Medical practitioners should advise patients about the potential for next day somnolence.

Driving ability was impaired in some subjects taking DAYVIGO 10. 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 section 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 medicine to treat insomnia is not recommended. Patients should be advised not to consume alcohol in combination with DAYVIGO because of additive effects *(see section 4.5)*

Because DAYVIGO can cause drowsiness, patients, particularly the elderly, are at a higher risk of falls (*see section 5.2 Elderly use*).

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. Medical practitioners 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 Behaviours

Complex sleep behaviours, 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 behaviours may occur following the first or any subsequent use of DAYVIGO, with or without the concomitant use of alcohol and other CNS depressants *(see section 4.5)*

Discontinue DAYVIGO immediately if a patient experiences a complex sleep behaviour.

Compromised Respiratory Function

The effect of DAYVIGO on respiratory function should be considered if prescribed to patients with

compromised respiratory function.

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

DAYVIGO has not been studied in patients with chronic obstructive pulmonary disease (COPD) or moderate to severe OSA. Clinically meaningful respiratory effects of DAYVIGO in COPD or moderate to severe OSA cannot be excluded.

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.

The emergence of any new behavioural 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 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 medicines such as DAYVIGO.

Abuse of DAYVIGO and dependence

Abuse

Abuse is the intentional, non-therapeutic use of a drug or medicine, even once, for its desirable psychological

or physiological effects. Abuse potential was analysed in a controlled trial that enrolled recreational hypnotic users, and the potential abuse of DAYVIGO 10 was found to be greater than that of placebo in the comparative trial (p-value: 0.995 that DAYVIGO 10 and placebo are not similar).

Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated medicine use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a medicine. In animal studies and clinical trials evaluating physical dependence, chronic administration of lemborexant did not produce withdrawal signs or symptoms upon medicine discontinuation. This suggests that lemborexant does not produce physical dependence.

Excipients

DAYVIGO contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicine on DAYVIGO

Strong, Moderate, and Weak CYP3A Inhibitors

Concomitant use with a strong (itraconazole, clarithromycin), moderate (fluconazole, verapamil), or weak (ranitidine) CYP3A inhibitor increases lemborexant AUC and C_{max} which may increase the risk of DAYVIGO adverse reactions *(see section 5.2 Pharmacokinetic properties).*

Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inhibitors. The maximum recommended dose of DAYVIGO with weak CYP3A inhibitors is 5 mg *(see section 4.2 Special populations).*

Strong and Moderate CYP3A Inducers

Concomitant use with a strong (rifampin, carbamazepine, St. John's wort) or moderate (efavirenz, modafinil) CYP3A inducer decreases lemborexant exposure, which may reduce DAYVIGO efficacy *(see section 5.2 Pharmacokinetic properties).*

Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inducers *(see section 4.2 Special populations)*.

Alcohol

Concomitant use of alcohol increases lemborexant C_{max} and AUC. Coadministration 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 section 5.1 Pharmacodynamic properties)*

Avoid alcohol consumption with DAYVIGO *(see section 4.4 Warnings and Special Precautions)*.

Effect of DAYVIGO on other medicine

CYP2B6 Substrates

Concomitant use of DAYVIGO decreases the AUC of medicine that are CYP2B6 substrates (bupropion, methadone), which may result in reduced efficacy for these concomitant medications *(see section 5.2 Pharmacokinetic properties)*.

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.

In Vitro Studies with Substrates of Transporters

Lemborexant and its major metabolite (M10) do not have the potential to inhibit P-gp, BCRP, BSEP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1, and MATE2-K.

4.6 Fertility, pregnancy and lactation

Pregnancy

DAYVIGO is not recommended in pregnancy. There are no available data on DAYVIGO use in pregnant women to evaluate for medicine-associated risks of major birth defects, miscarriage or adverse maternal or foetal 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 section 5.3 Data).*

Safety during pregnancy has not been established.

Breastfeeding

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 at concentrations higher than in maternal plasma. When a medicine is present in animal milk, it is likely that the medicine will be present in human milk. 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.

Safety during breastfeeding has not been established

4.7 Effects on ability to drive and use machines

Driving ability was impaired in some subjects taking DAYVIGO 10 mg *(see section 5.1, Special safety studies, Effects on driving).* 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 section 4.2).* If DAYVIGO is taken in these circumstances, patients should be cautioned against driving and other activities requiring complete mental alertness.

4.8 Undesirable effects

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.

a. Summary of the safety profile

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).

b. Tabulated list of adverse reactions

Table 1 presents the adverse reactions by MedDRA system organ class. The frequencies of the adverse reactions are 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 ≥2 % in DAYVIGO-treated patients and greater than in placebo-treated patients. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, ADRs are presented in order of decreasing seriousness. The frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1: Adverse reactions 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

MedDRA system organ class (SOC)	**Placebo**	**DAYVIGO**	
	n=528 (%)	5 mg n=580 (%)	10 mg n=582 (%)
Nervous system disorders			
Common: Somnolence or fatigue*	1,3	6,9	9,6
Common: Headache	3,4	5,9	4,5
Psychiatric disorders			
Common: Nightmare or abnormal	0,9	0,9	2,2

dreams			

* Combines preferred terms somnolence, lethargy, fatigue, sluggishness

c. Description of selected adverse reactions

CNS Depressant Effects and Daytime Impairment *(see section 4.4)*.

Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms *(see section 4.4)*.

Complex Sleep Behaviours *(see section 4.4)*.

Patients with Compromised Respiratory Function *(see section 4.4)*.

Worsening of Depression/Suicidal Ideation *(see section 4.4)*.

Other Adverse Reactions Observed During Clinical Trials (Studies 1 and 2)

Other adverse reactions of <2 % incidence but greater than placebo are shown below. The following list does not include adverse reactions 1) for which a medicine cause was remote, 2) that were so general to be uninformative, or 3) that were not considered to have clinically significant implications.

- Sleep paralysis was reported in 1,6 % and 1,3 % of patients receiving DAYVIGO 10 mg and 5 mg, respectively, compared to no reports for placebo. Hypnagogic hallucinations were reported in 0,7 % and 0,1 % of patients receiving DAYVIGO 10 mg and 5 mg, respectively, compared to no reports for placebo *(see section 4.4)*.
- Two events of complex sleep behaviour were reported, both in patients receiving DAYVIGO 10 mg *(see section 4.4)*.

Adverse Reactions Resulting in Discontinuation of Treatment during clinical trials

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).

d. Paediatric population

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

e. Other special populations

No adverse reactions that is applicable to a specific population were reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

There is limited clinical experience with DAYVIGO overdose. In clinical pharmacology studies, healthy subjects 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. In managing overdose, provide supportive care, including close medical supervision and monitoring and consider the possibility of multiple medicine involvement.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.2 Sedatives, hypnotics

ATC code: N05CM21 Other hypnotic and sedative drugs

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 signalling 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.

Antagonism of orexin receptors may also underlie potential adverse effects such as signs of narcolepsy/cataplexy. Lemborexant administered to mice at oral doses greater than 10 mg/kg resulted in behaviour characteristic of cataplexy when presented with chocolate.

Pharmacodynamic effects

Lemborexant binds to orexin receptors OX1R and OX2R and acts as a competitive antagonist (IC50 values of 6,1 nM and 2,6 nM, respectively). A major metabolite of lemborexant, M10, binds with comparable affinity as the parent medicine to orexin receptors OX1R and OX2R (IC_{50} values of 4,2 nM and 2,9 nM), respectively.

Cardiac Electrophysiology

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

Medicine 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 section 4.5)*.

Clinical efficacy and safety

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).

In Study 1, 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, sleep onset latency (sSOL), compared to placebo (Table 2). DAYVIGO 5 mg and 10 mg also showed statistically significant superiority in subject sleep efficiency (sSEF) and wake after sleep onset (sWASO).

Table 2: 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.

In Study 2, 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).

This study demonstrated that DAYVIGO 5 mg and 10 mg is statistically significant superiority on the primary efficacy measure, latency to persistent sleep (LPS), compared to placebo (Table 3). DAYVIGO 5 mg and 10 mg demonstrated statistically significant improvement in subjective sleep efficiency (SEF) and wake after sleep onset (WASO) compared to placebo.

Table 3: 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 10mg*	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.

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.

Night-time 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 night-time 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).

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 sleep onset latency (sSOL) and wake after sleep onset (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 medicine in patients who received DAYVIGO 5 mg or 10 mg. There was no evidence of withdrawal effects following DAYVIGO discontinuation at either dose.

5.2 Pharmacokinetic properties

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 %, $AUC_{0\text{-}inf}$ 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 1 970 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.

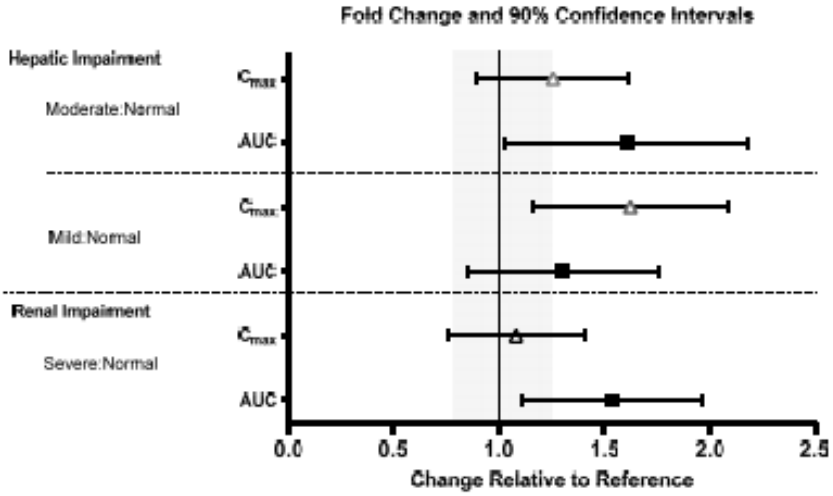
Excretion

Following administration of an oral dose, 57,4 % of the dose was recovered in the faeces 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 patient groups

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 paediatric 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



Elderly 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. Because DAYVIGO can increase somnolence and drowsiness, patients, particularly the elderly, are at a higher risk of falls (see section *CNS depressant effects and Daytime impairment* above). 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.

Hepatic Impairment

DAYVIGO has not been studied in patients with severe hepatic impairment. Use in this population is not

recommended.

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).

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.

Medicine Interaction Studies

The effects of other medicines on the exposures of lemborexant are summarized in Figure 2. The effects of lemborexant on the exposures of other medicines 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, medicine 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 Medicines on the Pharmacokinetics of Lemborexant 10 mg

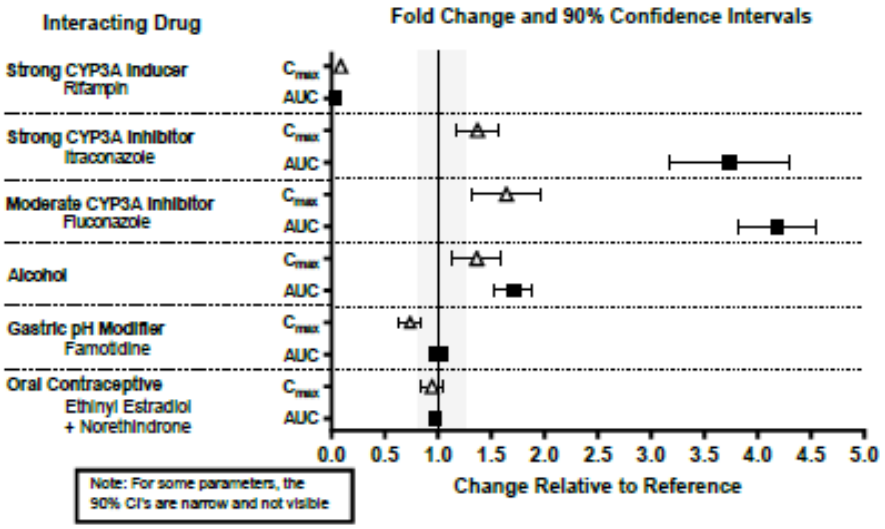
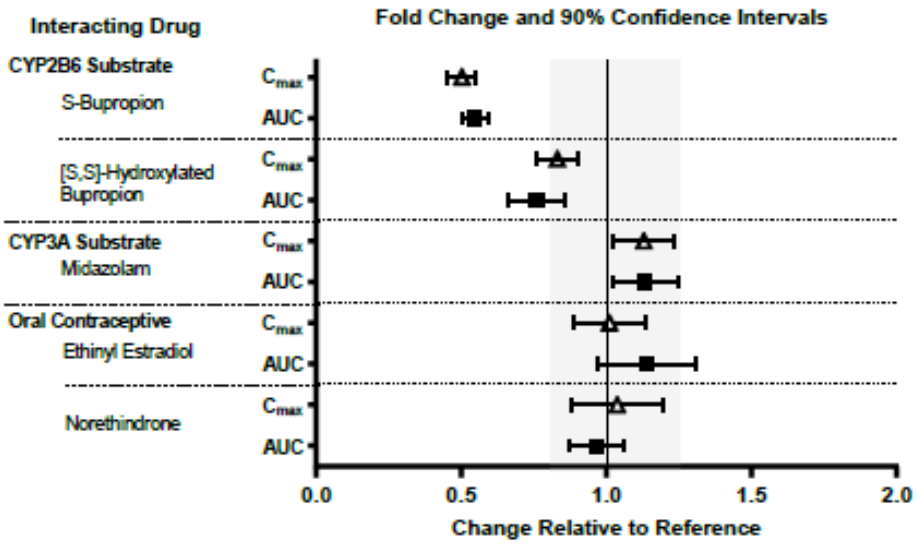


Figure 3. Effects of Lemborexant 10 mg on the Pharmacokinetics of Co-Administered Medicines



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.

5.3 Preclinical safety 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 foetal body weight, an increased number of dead foetuses, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

Hydroxypropyl cellulose

Lactose monohydrate

Low-substituted hydroxypropyl cellulose

Magnesium stearate

Film-coating:

Dayvigo 5: Opadry 03F42222 Yellow consisting of hypromellose 2910, talc, polyethylene glycol 800, titanium dioxide, ferric oxide yellow.

Dayvigo 10: Opadry 03F43101 Orange consisting of hypromellose 2910, talc, polyethylene glycol 800, titanium dioxide, ferric oxide yellow, ferric oxide red.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Store tablets in the original package until required for use.

6.5 Nature and contents of container

Polyvinyl chloride (PVC) film/aluminium foil blister strips in outer cardboard carton.

Pack sizes: 28 or 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Eisai Pharmaceuticals Africa (Pty) Ltd

2nd Floor, Golden Oak House,

Ballyoaks Office Park,

35 Ballyclare Drive

Bryanston,

Johannesburg

2191

8. REGISTRATION NUMBER(S)

DAYVIGO 5: 56/2.2/0571

DAYVIGO 10: 56/2.2/0572

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION