NEW ZEALAND DATA SHEET

1 PRODUCT NAME

DAYVIGO 5 mg film coated tablet.

DAYVIGO 10 mg film coated tablet.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mg DAYVIGO film coated tablet contains 5 mg lemborexant

Each 10 mg DAYVIGO film coated tablet contains 10 mg lemborexant

Excipient with known effect: contains lactose.

Each 5 mg tablet contains 93.9 mg of lactose (as monohydrate).

Each 10 mg tablet contains 88.9 mg of lactose (as monohydrate).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

DAYVIGO 5 mg film coated tablets are pale yellow, round, biconvex, film coated tablets, and debossed with "5" on one side and "LЄM" on the other side.

DAYVIGO 10 mg film coated tablets are orange, round, biconvex, film coated tablets, and debossed with "10" on one side and "LЄM" on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DAYVIGO is indicated for the treatment of insomnia, characterised by difficulties with sleep onset and/or sleep maintenance in accordance with latest Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose of DAYVIGO is 5 mg, taken no more than once per night and within a few minutes before going to bed, with at least 7 hours remaining before the planned time of

awakening. If the 5 mg dose is well-tolerated but greater effect is needed, the dose can be increased to 10 mg once daily, the maximum recommended dose. **DAYVIGO should be used at the lowest dose and for the shortest duration as clinically indicated.**

Time to sleep onset may be delayed if taken with or soon after a meal (see Section 5.2 Pharmacokinetic properties).

Patients should be advised not to consume alcohol in combination with DAYVIGO (see Section 4.5 Interactions with other medicines and other forms of interactions, Section 5.2 Pharmacokinetic properties).

Use with CYP3A Inhibitors

Co-administration with moderate or strong CYP3A inhibitors

Avoid concomitant use of DAYVIGO with moderate or strong CYP3A inhibitors (see Section 4.5 Interactions with other medicines and other forms of interactions, Section 5.2 Pharmacokinetic properties).

Co-administration with weak CYP3A inhibitors

The maximum recommended dose of DAYVIGO is 5 mg when co-administered with weak CYP3A inhibitors (see Section 4.5 Interactions with other medicines and other forms of interactions, Section 5.2 Pharmacokinetic properties).

Use with CYP3A Inducers

Co-administration with moderate or strong CYP3A inducers

Avoid concomitant use of DAYVIGO with moderate or strong CYP3A inducers (see Section 4.5 Interactions with other medicines and other forms of interactions, Section 5.2 Pharmacokinetic properties).

Special populations

Patients with renal impairment

No dose adjustment is required in patients with mild, moderate, or severe renal impairment (see Section 5.2 Pharmacokinetic properties).

Patients with hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment. The maximum recommended dose of DAYVIGO is 5 mg in patients with moderate hepatic impairment. DAYVIGO is not recommended in patients with severe hepatic impairment (see Section 5.2 Pharmacokinetic properties).

Elderly patients

There were no clinically meaningful differences in safety or effectiveness observed between elderly patients (≥ 65 years) and adult patients at the recommended doses (see Section 5.2 Pharmacokinetic properties). No dose adjustment is required in elderly patients.

Paediatric patients

Safety and effectiveness of DAYVIGO have not been established in paediatric patients (below 18 years of age). DAYVIGO is not recommended in paediatric patients (see Section 5.2 Pharmacokinetic properties).

Patients with compromised respiratory function

Obstructive Sleep Apnoea

Effects of DAYVIGO on respiratory function should be considered if prescribed to patients with compromised respiratory function. In a study of 39 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 decrease mean peripheral capillary oxygen saturation. In a study of 33 patients with moderate or severe obstructive sleep apnoea (apnoea-hypopnea index ≥ 15 events per hour of sleep), lemborexant did not increase the frequency of apnoeic events or decrease mean peripheral capillary oxygen saturation.

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

Chronic obstructive pulmonary disease

In a study of 30 patients with moderate or severe chronic obstructive pulmonary disease (COPD), overall, Lemborexant did not decrease mean peripheral capillary oxygen saturation and only numerically increased the frequency of apnoeic events.

DAYVIGO has not been studied in COPD patients with a FEV1 < 30% of predicted. Clinically meaningful respiratory effects of DAYVIGO in COPD cannot be excluded.

Method of administration

DAYVIGO is for oral use only.

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

4.3 CONTRAINDICATIONS

DAYVIGO, like other orexin receptor antagonists, is contraindicated in patients with narcolepsy.

Hypersensitivity to the active substance or to any of the excipients (see Section 6.1 List of excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

CNS depressant effects and daytime impairment

DAYVIGO, like other sleep-promoting drugs, may impair daytime wakefulness even when used as prescribed. Prescribers should advise patients about the potential for next-day somnolence. 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 the recommended dose is taken (see Section 4.2 Dose and method of administration). The use of DAYVIGO with other drugs to treat insomnia is not recommended.

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. CNS depressant effects may persist in some patients for up to several days after discontinuing DAYVIGO. The lowest effective dose for the patient should be used (see Section 4.2 Dose and method of administration).

Abuse

In an abuse liability study conducted in recreational sedative abusers (n=39), lemborexant (10, 20 and 30 mg) produced similar effects as zolpidem (30 mg) and suvorexant (40 mg) on subjective ratings of “Drug Liking”, “Overall Drug Liking”, “Take Drug Again.” and “Good Drug Effects” and other measures of subjective drug effects.

Abuse of DAYVIGO poses an increased risk of somnolence, daytime sleepiness, impaired reaction time and impaired driving skills. Patients at risk for abuse may include those with prolonged use of DAYVIGO, those with a history of drug abuse, and those who use DAYVIGO in combination with alcohol or other abused drugs.

Dependence

In both animal studies and clinical trials evaluating physical dependence, chronic administration of lemborexant did not produce withdrawal signs or symptoms upon drug discontinuation. This suggests that lemborexant does not produce physical dependence.

Use in hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment. The maximum recommended dose of DAYVIGO is 5 mg in patients with moderate hepatic impairment.

DAYVIGO is not recommended in patients with severe hepatic impairment (see Section 4.2 Dose and method of administration, Patients with hepatic impairment and Section 5.2 Pharmacokinetic properties, Patients with hepatic impairment).

Use in renal impairment

No dose adjustment is required in patients with mild, moderate, or severe renal impairment (see Section 4.2 Dose and method of administration, Patients with renal impairment and Section 5.2 Pharmacokinetic properties, Patients with renal impairment).

Use in the elderly

No clinically meaningful differences in safety or effectiveness were observed between these patients and younger patients at the recommended doses.

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 303 (the first 30 days) and Study 304, 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.

Paediatric use

There is no experience with DAYVIGO in paediatric patients. DAYVIGO is not recommended for children aged less than 18 years.

Effect on laboratory tests

In the pooled data from the two controlled studies in patients with insomnia, no clinically meaningful differences were observed between patients receiving DAYVIGO and those receiving placebo in routine serum chemistry, haematology, or urinalysis parameters.

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 unrecognised underlying psychiatric or medical disorder and can emerge during the course of treatment with sleep-promoting drugs such as DAYVIGO.

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Potential for other medicinal products to affect DAYVIGO

Weak, moderate and strong CYP3A inhibitors

Metabolism by CYP3A is the major elimination pathway of lemborexant. Co-administration of DAYVIGO with moderate CYP3A inhibitors (e.g., fluconazole) or strong CYP3A inhibitors (e.g., itraconazole) increased the exposure (AUC) of lemborexant by approximately 4-fold and C_{max} by 1.6-fold. Other moderate and strong inhibitors of CYP3A would be expected to have similar effects on plasma levels of lemborexant. (see Section 4.2 Dose and method of administration and Section 5.2 Pharmacokinetic properties).

Using a physiologically based pharmacokinetic (PBPK) model, a weak effect is predicted when weak CYP3A inhibitors (e.g., fluoxetine) are co-administered with DAYVIGO. Avoid concomitant use of DAYVIGO with moderate or strong CYP3A inhibitors. The recommended dose of DAYVIGO is 5 mg when co-administered with weak CYP3A inhibitors (see Section 4.2 Dose and method of administration, and Section 5.2 Pharmacokinetic properties).

Moderate and strong CYP3A inducers

Avoid co-administration of DAYVIGO with moderate or strong CYP3A inducers. Co-administration with a strong CYP3A inducer resulted in a 97% reduction in DAYVIGO systemic exposure. This may result in a decrease in efficacy (see Section 4.2 Dose and method of administration and Section 5.2 Pharmacokinetic properties).

In vitro studies with transporters

Lemborexant is a poor substrate of P-gp, but its major metabolite (M10) is a substrate of P-gp. Lemborexant and M10 are not substrates of BCRP, OATP1B1, or OATP1B3 (see Section 5.2 Pharmacokinetic properties).

Alcohol

Lemborexant C_{max} and AUC increased by 35% and 70%, respectively, when co-administered with alcohol. Lemborexant did not affect alcohol concentrations. Alcohol should not be consumed with DAYVIGO (see Section 4.2 Dose and method of administration, Section 4.5 Interactions with other medicines and other forms of interactions, Section 5.2 Pharmacokinetic properties).

Potential for DAYVIGO to affect other medicinal products

Clinical studies with substrates of CYP3A or CYP2B6

Lemborexant induced and inhibited CYP3A4 *in vitro*; however, this was not seen in clinical studies as shown by the absence of a drug-drug interaction with midazolam (a CYP3A4

substrate). Lemborexant weakly induces CYP2B6 based on study with bupropion as a CYP2B6 substrate. Substrates of CYP3A and CYP2B6 can be co-administered with DAYVIGO (see Section 5.2 Pharmacokinetic properties).

In vitro studies with substrates of CYP

In vitro, lemborexant has a potential to induce CYP3A and a weak potential to inhibit CYP3A and induce CYP2B6. Lemborexant and M10 do not have the potential to inhibit other CYP isoforms (see Section 5.2 Pharmacokinetic properties). Lemborexant does not induce CYP2C8, CYP2C9, and CYP2C19 at clinically relevant concentrations.

In vitro studies with substrates of transporters

Lemborexant and M10 do not have the potential to inhibit P-gp, BCRP, BSEP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT 2, MATE1, and MATE2-K (see Section 5.2 Pharmacokinetic properties).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Effects on fertility in humans are unknown.

In female rats orally administered lemborexant prior to and throughout mating and continuing to gestation Day 6, effects on female fertility (irregular oestrous cycle and decreased pregnancy rate) were observed at oral doses of 100 and 1000 mg/kg/day (approximately 60 and 545 times the exposure at the MRHD based on AUC). Decreased numbers of corpora lutea, implantations, and live embryos were noted at 1000 mg/kg/day. The NOAEL of 30 mg/kg/day is approximately 12 times the MRHD based on AUC. Lemborexant did not affect fertility when administered orally to male rats at doses resulting in exposures up to approximately 138 times the MRHD based on AUC.

Use in pregnancy

Pregnancy Category B3.

There are no adequate and well-controlled studies in pregnant women. DAYVIGO should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus.

Administration of lemborexant to pregnant rats during organogenesis in 2 separate studies at oral doses of 60, 200, and 600 mg/kg/day or 20, 60, and 200 mg/kg/day resulted in growth delays, embryofetal toxicity and malformations at maternal plasma exposures that were 388 times the plasma exposure at the maximum recommended human dose (MRHD) based on AUC. The maternal exposure at the no observed adverse effect level (NOAEL) (200 mg/kg/day) was 143 times the exposure at the MRHD based on AUC.

Administration of lemborexant to pregnant rabbits during organogenesis at oral doses of 10, 30, and 100 mg/kg/day resulted in a higher incidence of skeletal variations but no embryofetal toxicity or malformations at maternal exposures up to approximately 139 times the exposure at the MRHD based on AUC. The exposure at the NOAEL (30 mg/kg/day) was 23 times the exposure at the MRHD based on AUC.

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

Use in lactation

Data from a clinical lactation study show the presence of trace quantities of lemborexant in human milk. The relevant infant dose (RID) is approximately 2% of the maximum approved adult dose of 10 mg. A milk-only lactation study was conducted in 8 healthy, adult lactating women. The mean amount of lemborexant recovered in human milk was 0.0174 mg following a 10 mg maternal dose. The mean calculated daily infant oral dosage was 0.0029 mg/kg/day based on a nominal weight of 6 kg.

There are no data on the effects of lemborexant on the breastfed infant, or the effects on milk production. Infants exposed to DAYVIGO through breastmilk should be monitored for excessive sedation. The developmental and health benefits of 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 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.

4.8 UNDESIRABLE EFFECTS

Clinical trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of DAYVIGO was evaluated in 1418 adult patients with insomnia disorder (age 18 to 88 years) from two controlled efficacy trials (Study 303 and Study 304). Study 303 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-randomised to receive DAYVIGO 5 or 10 mg once nightly. In Study 303, 434 patients were treated with DAYVIGO for one year. Study 304 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 incidence of discontinuation due to adverse reactions for patients treated with 5 mg or 10 mg of DAYVIGO was 3.5% for 5 mg and 6.1% for 10 mg compared to 2.7% for placebo.

The most common adverse reaction leading to discontinuation was somnolence (DAYVIGO 5 mg 1.1%, DAYVIGO 10 mg 2.3%, placebo 0.6%).

Most common adverse reactions

In clinical trials of patients with insomnia treated with DAYVIGO 5 mg or 10 mg, the most common adverse reaction (reported in 5% or more of patients treated with DAYVIGO and at a higher rate than placebo) was somnolence (DAYVIGO 5 mg 6.6%, DAYVIGO 10 mg 10.5%, placebo 1.6%). DAYVIGO was associated with a dose-related increase in somnolence.

Table 1 shows adverse drug reactions (ADRs) by MedDRA system organ class. The frequency of the ADRs is based on pooled data from the first 30 days of the 6-month controlled period from Study 303 and the 1-month controlled efficacy study (Study 304). 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

	Placebo	DAYVIGO		Frequency category[1]
MedDRA preferred term	(n=528) n (%)	5 mg (n=580) n (%)	10 mg (n=582) n (%)	
Nervous system disorders				
Somnolence	7 (1.3)	29 (5.0)	48 (8.2)	Common
Headache	18 (3.4)	34 (5.9)	26 (4.5)	Common
Psychiatric disorders				
Nightmare or abnormal dreams	5 (0.9)	5 (0.9)	13 (2.2)	Common

[1] ADR frequencies are based upon the highest percentage rate seen in either lemborexant dose group.

Other adverse reactions

Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, can occur with the use of DAYVIGO. In clinical trials, DAYVIGO was associated with sleep paralysis: DAYVIGO 5 mg 1.1% or DAYVIGO 10 mg 1.6% compared to no reports for placebo.

Two events of complex sleep behaviour were reported, both in patients receiving DAYVIGO 10 mg.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

For information on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764766).

There is limited clinical experience with lemborexant 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 lemborexant showed dose-dependent increases in the frequency of somnolence. There is no available specific antidote to an overdose of lemborexant. In the event of overdose, standard medical practice for the management of any overdose should be used. A certified poison control centre should be contacted for updated information.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacotherapeutic group: Orexin receptor antagonist; Hypnotic; Sedative, ATC code: N05CJ02.

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 or 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. Chocolate is a stimulus that has been demonstrated to increase cataplexy occurrences in narcoleptic mice.

Pharmacodynamic effects

Cardiac electrophysiology

The effect of lemborexant on the QTc interval using a high precision analysis was measured in multiple dose studies in human patients administered daily doses up to 75 mg. The concentration-response relationship was analysed using a linear mixed-effects model. The model-predicted QTc effect at the highest observed concentration was 1.1 msec (90% CI: – 3.49 to 5.78), indicating that a QTc prolongation effect > 10 msec could be excluded at a dose 7.5-times the maximum recommended dose. Thus, lemborexant does not prolong the QTc interval at clinically relevant doses.

Clinical trials

Controlled clinical studies

DAYVIGO was evaluated in two clinical trials in patients with insomnia characterised by difficulties with sleep onset and/or sleep maintenance (Study E2006-G000-303 (Study 303)), and Study E2006-G000-304 (Study 304)).

Study 303 was a 6-month, randomised, double-blind, placebo-controlled, multi-centre trial in adult patients age 18 or older who met Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for insomnia disorder. Patients were randomised 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 303 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).

In Study 303, DAYVIGO 5 mg and 10 mg demonstrated statistically significant superiority on the primary efficacy measure, sSOL, compared to placebo (Table 2) from the beginning of treatment (first 7 days) and as measured at the end of 6 months of treatment). DAYVIGO 5 mg and 10 mg also showed statistically significant superiority in sSEF and sWASO (at the beginning of treatment and as measured at the end of 6 months of treatment).

Table 2: Sleep diary assessments of sleep parameters through month 6 in Study 303

	Placebo n=318	DAYVIGO 5 mg n=316	DAYVIGO 10 mg n=315	Difference between DAYVIGO and placebo	
				DAYVIGO	
				5 mg	10 mg
Sleep Onset (sSOL), minutes					
Baseline Geometric Mean (SD)	45 (32)	43 (31)	45 (33)		
Week 1 Geometric Mean Change from Baseline	-4	-12	-14	8	10
LSGM Ratio	0.931	0.728	0.701	0.781***	0.752***
Month 1 Geometric Mean Change from Baseline	-10	-16	-18	-6	-8
LSGM Ratio	0.786	0.637	0.605	0.810***	0.770***
Month 6 Geometric Mean Change from Baseline	-18	-24	-26	-6	-8
LSGM Ratio	0.618	0.453	0.433	0.732***	0.701***
Sleep Maintenance (sSE), %					
Baseline mean (SD)	61 (18)	63 (18)	62 (17)		
Week 1 LSM Change from Baseline (SER)	2 (1)	6 (1)	8 (1)	4*** (1)	6*** (1)
Month 1 LSM Change from Baseline (SER)	6 (1)	8 (1)	9 (1)	2*** (1)	4*** (1)
Month 6 LSM Change from Baseline (SER)	10 (1)	14 (1)	14 (1)	4*** (1)	5*** (1)
Sleep Maintenance (sWASO), minutes					
Baseline mean (SD)	132 (80)	133 (83)	137 (87)		
Week 1 LSM Change from Baseline (SER)	-5 (3)	-19 (3)	-21 (3)	-14*** (4)	-17*** (4)
Month 1	-17 (3)	-23 (3)	-24 (3)	-6 (4)	-7 (4)

Table 2: Sleep diary assessments of sleep parameters through month 6 in Study 303

	Placebo n=318	DAYVIGO 5 mg n=316	DAYVIGO 10 mg n=315	Difference between DAYVIGO and placebo	
				DAYVIGO	
				5 mg	10 mg
LSM Change from Baseline (SER)					
Month 6 LSM Change from Baseline (SER)	-29 (4)	-47 (4)	-42 (4)	-18*** (5)	-13* (5)

LSGM: Least squares geometric mean; LSM: Least squares mean; SD: standard deviation; SER; standard error
**P < 0.05; **P < 0.01; ***P < 0.001*

Study 304 was a 1-month, randomised, double-blind, placebo- and active-controlled, multi-centre, 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 randomised to placebo (n=208), DAYVIGO 5 mg (n=266) or 10 mg (n=269), or zolpidem tartrate extended release (ER; 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 304 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. An additional prespecified key secondary endpoint compared DAVIGO 5 mg and 10 mg with zolpidem ER on wake after sleep onset in the second half of the night (WASO2H), as assessed by polysomnography.

The demographic and baseline characteristics of patients in Study 304 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 304, DAYVIGO 5 mg and 10 mg demonstrated statistically significant superiority on the primary efficacy measure, LPS, compared to placebo at the end of month of treatment, and also across the first 2 nights of dosing (Table 3).

Table 3: Polysomnographic assessments of sleep parameters in Study 304

	Placebo n=208	DAYVIGO		Difference between DAYVIGO and placebo	
		5 mg n=266	10 mg n=269	DAYVIGO	
				5 mg	10 mg
Sleep Onset (LPS), minutes					
Baseline Geometric Mean (SD)	34 (26)	33 (27)	33 (27)		
Days 1/2 Geometric Mean Change from Baseline	-7	-11	-13	-4	-6
LSGM Ratio	0.763	0.649	0.607	0.850**	0.795***
Month 1 Geometric Mean Change from Baseline	-8	-14	-16	-12	-13
LSGM Ratio	0.699	0.541	0.506	0.773***	0.723***
Sleep Maintenance (SE), %					
Baseline Mean (SD)	69 (10)	68 (11)	68 (11)		
Days 1/2 LSM Change from Baseline (SER)	5 (1)	14 (0)	17 (0)	9*** (1)	12*** (1)
Month 1 LSM Change from Baseline (SER)	6 (1)	13 (1)	14 (1)	7*** (1)	8*** (1)
Sleep Maintenance (WASO), minutes					
Baseline Mean (SD)	112 (37)	113 (39)	115 (40)		
Days 1/2 LSM Change from Baseline (SER)	-18 (2)	-51 (2)	-60 (2)	-33*** (3)	-42*** (3)
Month 1 LSM Change from Baseline (SER)	-21 (2)	-45 (2)	-47 (2)	-24*** (3)	-25*** (3)
Sleep Maintenance (WASO2H), minutes					
Baseline Mean (SD)	74 (30)	77 (33)	77 (32)		
Days 1/2	-9 (2)	-30 (2)	-37 (2)	-22*** (2)	-28*** (2)

Table 3: Polysomnographic assessments of sleep parameters in Study 304

	Placebo n=208	DAYVIGO		Difference between DAYVIGO and placebo	
		5 mg n=266	10 mg n=269	DAYVIGO	
				5 mg	10 mg
LSM Change from Baseline (SER)					
Month 1 LSM Change from Baseline (SER)	-11 (2)	-27 (2)	-29 (2)	-16*** (2)	-18*** (2)

LSGM: Least squares geometric mean; LSM: Least squares mean; SD: standard deviation; SER: Standard error;
**P < 0.05; **P < 0.01; ***P < 0.001*

Examination of subgroups by age, race, and sex did not suggest differences in response to DAYVIGO in either study.

Special safety studies

Middle of the night safety in older patients (age 55 years and older)

The effect of DAYVIGO was evaluated in a randomised, placebo- and active-controlled trial with a scheduled awakening 4 hours after the start of the 8-hour time in bed. Postural stability, the ability to awaken in response to a sound stimulus, and attention and memory were tested following the awakening. The comparator in the study, zolpidem tartrate ER, showed a statistically significant decrease in postural stability (increased body sway) compared to both lemborexant and placebo. There were no statistical differences between lemborexant and placebo on the ability to awaken in response to sound. There were no meaningful differences between lemborexant 5 mg and placebo on measures of attention and memory.

Effects on next-day postural stability and memory

The effects of DAYVIGO on next day postural stability and memory were evaluated in two randomised, 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.

Effects on driving

A randomised, 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). 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. The results of a symmetry analysis support the findings from the primary outcome

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 Study 303 (12 months) and Study 304 (1 month). 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 303 and 304, 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.

Respiratory safety

Healthy subjects with normal respiratory function

In a randomised, placebo-controlled, single-dose crossover study of 17 healthy adult and elderly subjects, there were no differences between placebo and DAYVIGO 10 mg and 25 mg with respect to mean peripheral capillary oxygen saturation.

Patients with mild, moderate or severe obstructive sleep apnoea (OSA)

In a randomised, placebo-controlled crossover study of 39 patients with mild OSA (apnoea-hypopnoea index > 5 and < 15 events per hour of sleep), overall, DAYVIGO did not increase the frequency of apnoeic events or decrease mean peripheral capillary oxygen saturation when compared with placebo following single and multiple doses of 10 mg.

In a randomised, placebo-controlled crossover study of 33 patients with moderate or severe OSA, overall, lemborexant did not increase the frequency of apnoeic events or decrease mean peripheral capillary oxygen saturation following single or multiple doses of 10 mg.

Patients with moderate or severe chronic obstructive pulmonary disease (COPD)

In a randomised, placebo-controlled crossover study of 30 patients with moderate or severe COPD, overall, lemborexant did not lead to a statistically significant increase in the frequency of apnoeic events or decrease mean peripheral capillary oxygen saturation following single or multiple doses of 10 mg.

DAYVIGO has not been studied in COPD patients with a FEV1 < 30% of predicted. Clinically meaningful respiratory effects of DAYVIGO in COPD cannot be excluded.

Daily functioning

In Study 303 and Study 304, the effect of DAYVIGO on daily functioning was assessed by scores on the Insomnia Severity Index (ISI). For patients treated with DAYVIGO, the ISI score decreased significantly compared to placebo, indicating that patients treated with DAYVIGO reported improvement of functional impairment.

Sleep stages

In Study 304, sleep stages for patients treated with DAYVIGO were assessed by polysomnography. DAYVIGO demonstrated a significant increase in rapid eye movement (REM) sleep compared to placebo and to zolpidem tartrate ER.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In healthy patients, the pharmacokinetic profile of lemborexant was examined after single doses of up to 200 mg and after once-daily administration of up to 75 mg for 14 days. Lemborexant is rapidly absorbed, with a time to peak concentration (t_{max}) of approximately 1 to 3 hours. Lemborexant exhibits linear pharmacokinetics with multi-exponential decline in plasma concentrations. The extent of accumulation of lemborexant at steady-state is 1.5- to 2-fold across the dose range. The effective half-life for 5 mg and 10 mg is 17 and 19 hours respectively. The plasma concentration at 9 hours after administration is approximately 10% to 13% of the C_{max}.

Ingestion of DAYVIGO with a high-fat meal resulted in a slight decrease in the rate of absorption as demonstrated by 23% decrease in C_{max} and delay in t_{max} of 2 hours and 18% increase in total exposure AUC.

Distribution

The volume of distribution of lemborexant is 1970 L. Plasma protein binding of lemborexant is approximately 88% *in vitro* and 94% in clinical samples. The blood to plasma concentration ratio of lemborexant is 0.65.

Metabolism

Lemborexant is primarily metabolised by CYP3A4 and to a lesser extent by CYP3A5. M10 is the only major circulating metabolite (12% of parent). The contribution of this metabolite to the pharmacological activity of lemborexant is low.

Excretion

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

Special Populations

Age, sex, race/ethnicity and BMI

No clinically significant differences in the pharmacokinetics of lemborexant were observed based on age, sex, race/ethnicity, or body mass index.

Elderly patients

Based on a population pharmacokinetic analysis in patients receiving 5 or 10 mg DAYVIGO once daily, apparent clearance was 26% lower in elderly (> 65 years of age). However, this effect was not clinically relevant (see Section 4.2 Dose and method of administration).

Paediatric patients

No studies have been conducted to investigate the pharmacokinetics of lemborexant in paediatric patients (see Section 4.2 Dose and method of administration).

Patients with renal impairment

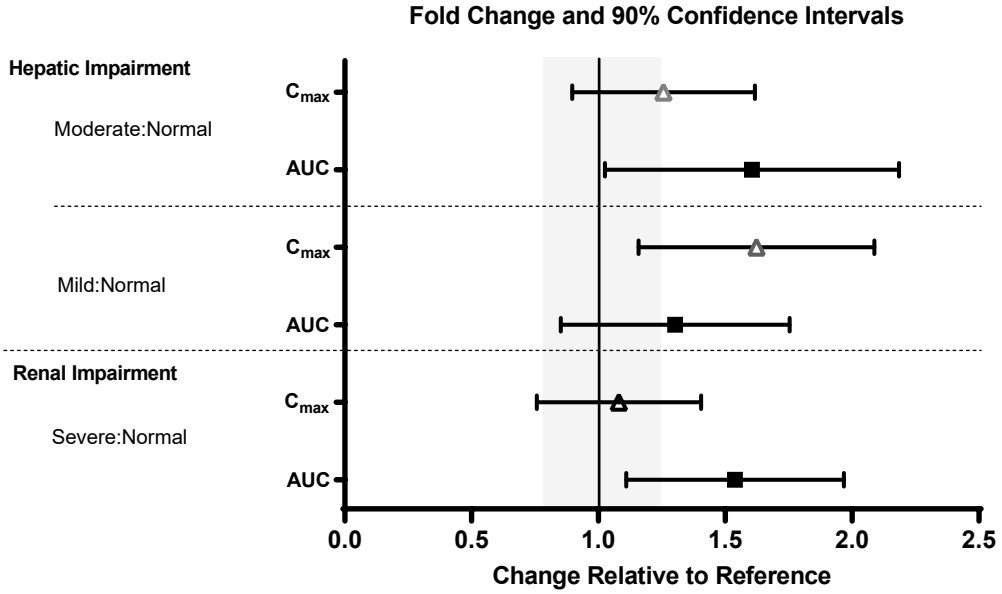
Severe renal impairment (urinary creatinine clearance ≤ 30 mL/min/1.73m^2) increased lemborexant exposure (AUC) 1.5-fold but had no effect on C_{max}. No dose adjustment is required in patients with renal impairment (see Section 4.2 Dose and method of administration).

Patients with hepatic impairment

Lemborexant has not been studied in patients with severe hepatic impairment. Use in this population is not recommended. Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic insufficiency increased lemborexant AUC and C_{max} by 1.5-fold. Terminal half-life was only increased in patients with moderate hepatic impairment (Child-Pugh B). No relationship between these findings and hepatic function was observed. No dose adjustment is required in patients with mild hepatic impairment. A maximum dose of 5 mg is recommended in patients with moderate hepatic impairment (see Section 4.2 Dose and method of administration).

Exposures of lemborexant in patients with hepatic and renal impairment are summarised in Figure 1.

Figure 1: Effects of hepatic and renal impairment on lemborexant pharmacokinetics



Drug interaction studies

The effects of other drugs on lemborexant

The effects of other drugs on the pharmacokinetics of lemborexant (10 mg) are presented in Figure 2 as change relative to lemborexant alone (test/reference). Based on these results, drug interactions between lemborexant and strong CYP3A inducers, strong CYP3A inhibitors, and moderate CYP3A inhibitors, are clinically significant.

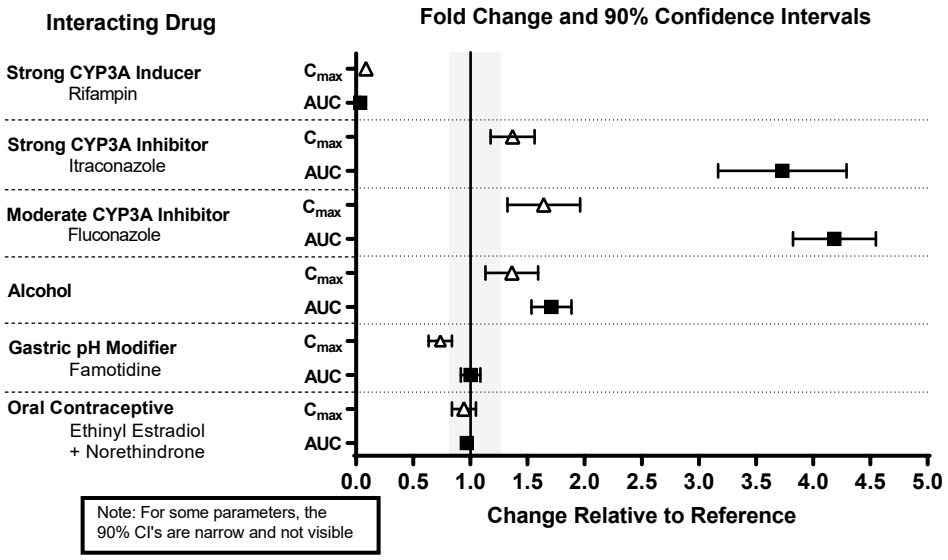
Using a physiologically based pharmacokinetic (PBPK) model, a weak effect is predicted when weak CYP3A inhibitors (e.g., fluoxetine) are co-administered with lemborexant. Co-administration of moderate (e.g., fluconazole) or strong (e.g., itraconazole) CYP3A inhibitors significantly increased lemborexant exposure. CYP3A inducers (e.g., rifampin) significantly decreased lemborexant exposure.

There was no evidence of an additive effect on impairing postural stability (as evidenced by body sway) when lemborexant was co-administered with alcohol; lemborexant did not impact postural stability when dosed alone. An additive negative effect on cognitive performance was observed up to 6 hours post dose when lemborexant 10 mg was co-administered with a single dose of alcohol (0.6 g/kg for females and 0.7 g/kg for males)

Co-administration of an H2 blocker (famotidine) with lemborexant decreased C_{max} by 27% and delayed t_{max} by 0.5 hours, but had no statistically significant effect on overall lemborexant exposure (AUC). A population analysis of Phase 1-3 data also showed no effect of proton pump inhibitors (PPIs) on apparent clearance of lemborexant. A pooled analysis of data from patients taking PPIs or H2 blockers in Study 303 and 304 showed that there was no effect on sleep latency or on safety parameters. Thus, lemborexant can be co-administered with gastric acid-reducing agents (PPIs or H2 blockers).

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

Figure 2: Effects of co-administered drugs on the pharmacokinetics of lemborexant 10 mg



Effects of lemborexant on other drugs

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

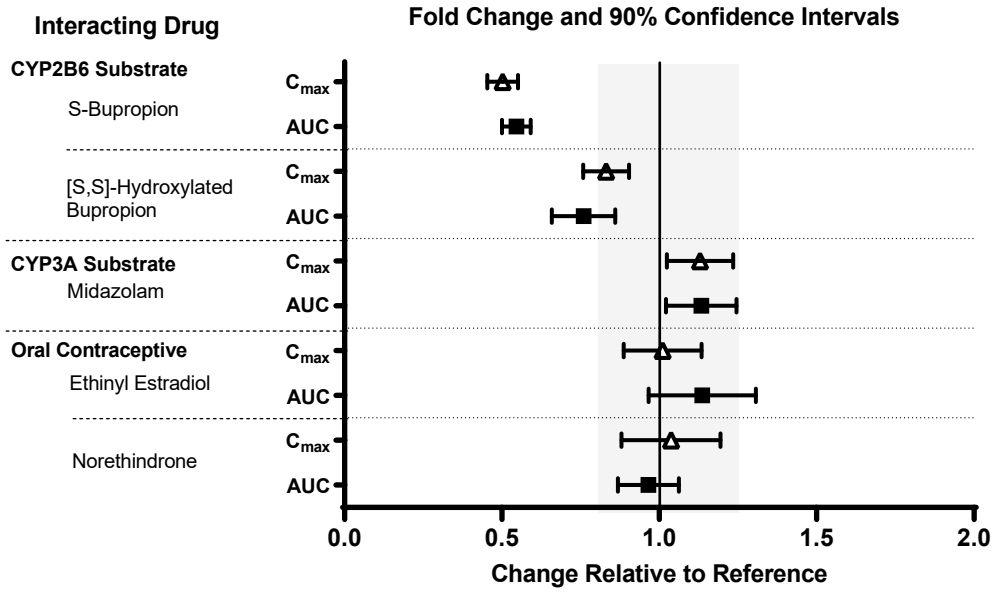
Lemborexant and M10 are not substrates of BCRP, OATP1B1, or OATP1B3 (see Section 4.5 Interactions with other medicines and other forms of interactions).

Specific *in vivo* effects of lemborexant (10 mg) on the pharmacokinetics of bupropion, oral contraceptives, and midazolam are presented in Figure 3 as a change relative to the interacting drug administered alone (test/reference). Based on these results, drug interactions between lemborexant and CYP2B6 substrates are expected to be clinically significant, but clinically, lemborexant weakly induces CYP2B6. Lemborexant is expected to have minimal effect on the pharmacokinetics of CYP2C8, CYP2C9, or CYP2C19 substrates.

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

Clinical studies with substrates of CYP3A or CYP2B6: Despite the *in vitro* findings, lemborexant does not induce or inhibit CYP3A4. Lemborexant weakly induces CYP2B6 (e.g., bupropion is CYP2B6 substrate). CYP3A and CYP2B6 substrates can be co-administered with lemborexant.

Figure 3: Effects of lemborexant 10 mg on the pharmacokinetics of co-administered drugs



5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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.

Carcinogenicity

Lemborexant did not increase the incidence of tumours 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 tumours in Tg ras H2 mice treated for 26 weeks at oral doses of 50, 150, and 500 mg/kg/day, which are estimated up to ≥ 47 times the MRHD based on AUC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The film coated tablets contain the excipients lactose monohydrate, hyprolose, magnesium stearate, Opadry complete film coating system (5 mg) and Opadry complete film coating system 03F43101 Orange (10 mg).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

5 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

Store in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

DAYVIGO 5 mg is available in PVC/aluminium blister pack containing 3 tablets or 28 tablets.
DAYVIGO 10 mg is available in PVC/aluminium blister packs containing 28 tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE (POISON STANDARD)

Prescription Medicine.

8 SPONSOR

Eisai New Zealand Ltd.
Simpson Grierson, Level 27
88 Shortland Street, Auckland Central
Auckland, 1010, NZ
0800 00 52 06
medinfo_newzealand@eisai.net

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to first distribute the medicine: 05 December 2024.

10 DATE OF REVISION

22 November 2024

Summary Table of changes

Version Number	Section changed	Summary of new information
1		New Data Sheet