Summary Report of Benefit-Risk Assessment

DAYVIGO FILM-COATED TABLET 5MG AND 10MG

NEW DRUG APPLICATION

Active Ingredient(s)	Lemborexant
Product Registrant	Eisai (Singapore) Pte Ltd
Product Registration Number	SIN16320P (5mg), SIN16321P (10mg)
Application Route	Abridged evaluation
Date of Approval	15 Sep 2021

A INTRODUCTION

Dayvigo is indicated for the treatment of adult patients with insomnia, characterised by difficulties with sleep onset and/or sleep maintenance.

The active substance, lemborexant, is an orexin receptor antagonist that blocks the binding of wake-promoting neuropeptides orexin A and orexin B to orexin receptors 1 and 2 (OX1R and OX2R), which is thought to suppress wake drive and promote normal sleeping.

Dayvigo is available as film coated tablets containing 5 mg or 10 mg of lemborexant. Other ingredients in the tablet core are magnesium stearate, low substituted hydroxypropylcellulose, lactose hydrate, and hydroxypropylcellulose. Ingredients in the film coating include yellow ferric oxide, titanium oxide, talc, hypromellose, and macrogol 6000 for the 5 mg tablet and yellow ferric oxide, red ferric oxide, titanium oxide, talc, hypromellose, macrogol 6000 for the 10mg tablet.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, lemborexant, is manufactured at Eisai Co., Ltd., Ibaraki-ken, Japan. The drug product, Dayvigo, is manufactured at Eisai Manufacturing Limited, Hertfordshire, United Kingdom.

Drug substance:

Adequate controls have been presented for the starting materials and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for Eisai Co., Ltd. are adequate to support the approved storage condition and re-test period. The packaging is double polyethylene bags within a steel, fibre, or plastic drum. The drug substance is approved for storage at or below 30°C with a re-test period of 36 months.

Drug product:

The tablet is manufactured using a wet granulation approach, followed by film-coating. The process is considered to be a standard process.

The drug product manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies are conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted are adequate to support the approved shelf-life of 36 months when stored at or below 30ºC. The container closure system is a PVC film/aluminium foil blister sheet containing 14 tablets.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of lemborexant was based primarily on two pivotal Phase 3 studies 303 and 304. These were multicentre, randomised, double-blind, placebo/active controlled, parallel group studies in adult patients who met DSM-5 criteria for insomnia disorder.

In Study 303, a total of 971 adult patients were randomised in a 1:1:1 ratio to receive lemborexant 5mg, 10mg or placebo, taken orally each night before the subject intended to try to sleep. 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 the change from baseline to end of treatment at 6 months for patient-reported sleep efficiency (sSE) and wake after sleep onset (sWASO). Both primary and secondary endpoints were based on patient reported electronic sleep diaries.

There were 323 patients each in the lemborexant 5mg and 10mg arms and 325 patients in the placebo arm. The majority of subjects were female (68.2%), white (71.5%) with a median age of 55 years (18-88 years). Of the non-white patients, 17% were Japanese, 0.4% were Chinese and 1.4% were Other Asians. 27.6% of patients were elderly who were 65 years or older.

A statistically significant improvement in the primary endpoint of sSOL was demonstrated for patients in the lemborexant 5mg and 10mg arms compared to placebo arm ($p<0.0001$) with a median change from baseline at Month 6 of -21.81 minutes, -28.21 minutes and -11.43 minutes, respectively.

Summary of results in Study 303

Primary efficacy endpoint: Change from baseline in sSOL at month 6			
	Placebo (n=318)	**Lemborexant 5mg (n=316)**	**Lemborexant 10mg (n=315)**
Baseline (median/min)	55.86	53.57	55.71
Median change from baseline/min	-11.43	-21.81	-28.21
Least squares geometric mean ratio (LSGM) vs placebo	-	0.732	0.701
95% CI, p value	-	0.636, 0.843 p<0.0001	0.607, 0.810 p<0.0001
Key secondary endpoints			
Change in sSE from baseline at Month 6			
Baseline (mean/%)	61.34	63.14	62.03
Mean change from baseline/%	10.36	15.34	15.55
LS mean treatment difference vs placebo/%	-	4.549	4.667
95% CI, p value	-	2.236, 6.861p=0. 0001	2.373, 6.960 p<0.0001
Change in sWASO from baseline at Month 6			
Baseline(mean/min)	132.49	132.77	136.83
Mean change from baseline/min	-32.14	-51.45	-48.12
LS Mean treatment difference vs placebo/min	-	- 17.474	- 12.671
95% CI, p value		-27.306, -7.643 p=0.0005	-22.378, -2.964 p=0.0105

Statistical superiority was also shown for the key secondary endpoints sSE and sWASO. The mean change in sSE from baseline at month 6 was statistically significantly greater with lemborexant 5mg (15.34%) and 10mg (15.55%) compared to placebo (10.36%). The LS mean treatment difference compared to placebo was 4.549% (p=0.0001) and 4.667% (p<0.0001) for lemborexant 5mg and 10mg respectively, indicating an improvement in sleep efficiency in the lemborexant arms.

The mean change in sWASO at month 6 was also greater with lemborexant 5mg (-51.45 minutes) and 10mg (-48.12 minutes) compared to placebo (-32.14 minutes). The LS mean treatment difference compared to placebo was -17.474 minutes (p=0.0005) and -12.671 minutes(p=0.0105) for lemborexant 5mg and 10mg respectively, indicating a greater reduction in subjective wakefulness after sleep onset.

In Study 304, a total of 1006 patients with insomnia aged 55 years and older were randomised in a 5:5:5:4 ratio to receive lemborexant 5mg, 10mg, zolpidem tartrate extended release (ER) 6.25mg or placebo, taken orally each night for 30 consecutive nights. The primary efficacy endpoint was the mean change from baseline in log-transformed latency to persistent sleep (LPS) from baseline to end of treatment (Days 29/30) in comparison to placebo, as measured by overnightpolysomnography (PSG). 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 were the mean change from baseline to end of treatment (Days 29/30) in sleep efficiency (SE) and wake after sleep onset (WASO) measured by PSG.

There were 269 subjects in the lemborexant 10mg arm and 266 subjects in the lemborexant 5mg arm, while 263 and 208 patients were randomized to the zolpidem ER 6.25mg and placebo treatment arms respectively. The majority of patients were female (86.4%) and white (72.3%) with a median age of 63.0 years (55-88 years). There were very few Asian patients in this study (0.2% Japanese, 0.2% Chinese and 1.0% Other Asian). 45% were at least 65 years of age, among which 7.8% were at least 75 years old.

A statistically significant improvement in the primary endpoint of LPS on Days 29/30 was demonstrated for patients in the lemborexant 5mg and 10mg arms compared to placebo ($p=0.0003$ and $p<0.0001$, respectively) with an improvement of -12.00 minutes, -16.25 minutes and -6.63 minutes respectively. In addition, the reduction from baseline in LPS was numerically greater in the lemborexant 5mg and 10mg arms compared to zolpidem ER with an improvement of -12.00 minutes, -16.25 minutes and -2.88 minutes respectively.

Summary of results in study 304

Primary efficacy endpoint results in Study 304 (change from baseline in LPS at Day29/30)

Primary efficacy endpoint: Change from baseline in LPS at Day 29/30				
	Placebo (n=208)	**Zolpidem ER 6.25mg (n=263)**	**Lemborexant 5mg (n=266)**	**Lemborexant 10mg (n=269)**
Baseline (median/min)	33.63	31.50	33.13	38.50
Median change from baseline/min	-6.63	-2.88	-12.00	-16.25
Least squares geometric mean ratio (LSGM) vs placebo	-	1.218	0.773	0.723
95% CI, p value	-	1.057, 1.403 p=0.0063	0.672, 0.889 p=0.0003	0.628, 0.832 p<0.0001
Key secondary endpoints				
Change in SE from baseline at Day 29/30				
Baseline(mean/%)	68.89	68.13	68.36	67.85
Mean change from baseline/%	5.35	9.06	12.93	14.09
LS mean treatment difference/%	-	3.15	7.07	8.03
95% CI, p value	-	1.67, 4.63 p<0.0001	5.61, 8.54 p<0.0001	6.57, 9.49 p<0.0001
Change in WASO from baseline at Day 29/30				
Baseline (mean/min)	111.75	114.31	113.44	114.83

Mean change from baseline/min	-18.58	-36.50	-43.89	-46.43
LS mean treatment difference/min	-	-16.25	-23.96	-25.35
95% CI, p value	-	-22.31, -10.18 p<0.0001	-29.98, -17.95 p<0.0001	- 31.36, -19.34 p<0.0001

Statistical superiority in comparison to placebo was also demonstrated for the secondary endpoints SE and WASO. The mean change from baseline in SE on Days 29/30 was statistically significantly greater for lemborexant 5mg (12.93%) and lemborexant 10mg (14.09%), compared to placebo (5.35%). The LS mean treatment difference compared to placebo was 7.07% (p<0.0001) and 8.03% (p<0.0001) for lemborexant 5mg and 10mg respectively. The mean change in WASO on Days 29/30 was also greater for lemborexant 5mg (-43.89 minutes) and 10mg (-46.43 minutes) compared to placebo (-18.58 minutes). The LS mean treatment difference compared to placebo was -23.96 minutes (p<0.0001) and -25.35 minutes (p<0.0001) for lemborexant 5mg and 10mg respectively. Consistent numerical improvements were also observed for both lemborexant arms compared to zolpidem ER for both SE and WASO.

Overall, Study 303 demonstrated statistically significant and clinically meaningful improvements of patient-reported end points of sleep onset, sleep efficiency, and wake-after-sleep onset for both doses of lemborexant (5mg and 10mg) compared with placebo. These results were also supported by statistically significant improvements compared to placebo based on objective measurements using PSG in Study 304. A numerical benefit was observed for the higher 10mg dose for some of the key parameters, and this dose may be considered for patients who do not respond adequately to the 5mg dose.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of lemborexant was based primarily on safety data derived from Study 303 and 304. In Study 303, 314 patients each were exposed to lemborexant 5mg and 10mg and 319 patients were exposed to placebo during the placebo-controlled period. The median duration of exposure was 180 days for placebo and lemborexant 5mg arms and 179.5 days for lemborexant 10mg arm. In Study 304, 266 and 268 patients were exposed to lemborexant 5mg and 10mg respectively, 209 patients were exposed to placebo and 263 patients to zolpidem ER. The median duration of exposure was 30 days across all arms.

Overview of safety profile in Study 303 (6 month placebo controlled period)

	Placebo (n=319)	**Lemborexant 5mg (n=314)**	**Lemborexant 10mg (n=314)**
Any adverse events (AE)	200 (62.7%)	192 (61.1%)	187 (59.6%)
Treatment-related AE	44 (13.8%)	78 (24.8%)	91 (29.0%)
Severe AEs	10 (3.1%)	13 (4.1%)	8 (2.5%)
SAEs	5 (1.6%)	7 (2.2%)	9 (2.9%)
Deaths due to AE	0	0	0
AEs leading to study drug discontinuation	12 (3.8%)	13 (4.1%)	26 (8.3%)

Overview of safety profile in Study 304

	Placebo (n=209)	Zolpidem ER 6.25mg (n=263)	Lemborexant 5mg (n=266)	Lemborexant 10mg (n=268)
Any AE	53 (25.4%)	93 (35.4%)	74 (27.8%)	82 (30.6%)
Treatment-related AE	16 (7.7%)	40 (15.2%)	30 (11.3%)	39 (14.6%)
Severe AEs	3 (1.4%)	8 (3.0%)	1 (0.4%)	2 (0.7%)
SAEs	0	4 (1.5%)	2 (0.8%)	0
Deaths due to AE	0	0	0	0
AEs leading to study drug discontinuation	2 (1.0%)	7 (2.7%)	2 (0.8%)	3 (1.1%)

In Study 303, the common treatment-related AEs (≥2%) included somnolence (8.6%), headache (3.8%), fatigue (3.2%), and abnormal dreams (2.2%) in the lemborexant 5mg arm, and somnolence (12.7%), headache (3.8%), fatigue (2.5%), and nightmare (2.2%) in the lemborexant 10mg arm. A similar safety profile was reported in the short-term Study 304.

The main AE of special interest reported with lemborexant was somnolence. In Study 303, there was a dose-dependent increase in treatment-related somnolence in the lemborexant arms (1.3% in the placebo arm, 8.6% in the lemborexant 5mg arm, and 12.7% in the lemborexant 10mg arm). In Study 304, the rates were 1.4%, 1.5%, 3.8% and 6.3% for placebo, zolpidem, lemborexant 5mg and lemborexant 10mg respectively.

In Study 303, somnolence was also more frequently reported in subjects ≥65 years in the lemborexant 10 mg treatment arm compared to individuals younger than 65 (19.0% vs 10.9% respectively) orto subjects ≥65 years in the lemborexant 5 mg arm (8.1%). In view of the observed dose- dependent increase in somnolence, lemborexant is recommended to be taken at an initial doseof 5mg once nightly before bedtime, and adjusted as appropriate to a maximum of 10mg in accordance with clinical response and tolerability.

Other rare (<1%) but potentially clinically significant adverse reactions included sleep paralysis, hypnagogic hallucinations, falls, and cataplexy-like symptoms. The incidence of cataplexy-like events was low in both pivotal studies (0.3% for lemborexant 10mg arm in Study 303 and none in Study 304), but none was adjudicated as cataplexy. These AEs have been adequately described as warnings and precautions in the proposed package insert.

The rates of suicidal ideation assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) were low and comparable between treatment arms and placebo (0.4%, 0% and 0.4% for placebo, lemborexant 5mg and lemborexant 10mg respectively at 6-months in Study 303; 0.5%, 1.1%, 0.4% and 0.4% for placebo, zolpidem, lemborexant 5mg and lemborexant 10mg respectively on Day 31 in Study 304). There were no reports of suicidal or self-injurious behaviour. Treatment with lemborexant may be associated with the potential risk of abuse and individuals with a history of abuse or addiction to alcohol or other drugs should be carefully monitored while on lemborexant treatment

Overall, the safety profile of lemborexant was as expected and the incidence was similar to the other drugs used for insomnia. Appropriate warnings and precautions have been included in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Insomnia is associated with impairments in multiple aspects of daily functioning as well as other medical comorbidities. The current treatment of insomnia includes benzodiazepines and melatonin receptor agonists. There is a clinical need for a noveltreatment option for insomnia, which adequately addresses both sleep initiation and maintenance, especially for older patients who commonly have sleep maintenance difficulties.

Studies 303 and 304 demonstrated efficacy for faster sleep initiation and maintenance of sleep with lemborexant 5mg and 10mg compared to placebo based on both subjective sleep diary and objective PSG parameters. Long term efficacy of up to 6 months was demonstrated in Study 303 compared with placebo. Overall, there was a numerical improvement in efficacy in the lemborexant 10mg arm compared to the 5mg arm.

Lemborexant was generally well-tolerated in the clinical studies. Somnolence was the most commonly reported AE associated with lemborexant, and its incidence appeared to be dose-related. The AEs of special interest have been adequately described in the relevant warnings and precautions section of the product label. In view of the numerical clinical benefit and dose-dependent AEs associated with the higher 10mg dose, the recommended starting dose is 5mg once daily at bedtime, to be adjusted accordingly to patient response and tolerability up to a maximum of 10mg.

Overall, the benefit-risk profile of lemborexant in the treatment of insomnia was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of lemborexant for the treatment of insomnia was deemed favourable and approval of the product registration was granted on 15 Sep 2021.