hhc

human health care


START YOUR DAY
WITH VIGOR
DAYVIGO® is a dual orexin receptor antagonist (DORA) indicated for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.
Hi-Eisai
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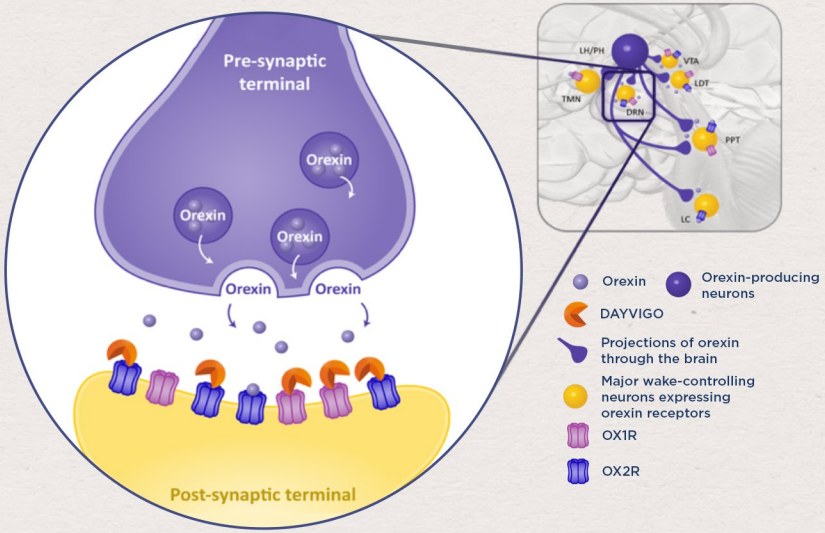
human health care
lemborexant
DAYVIGO
5mg Film-Coated Tablet
Orexin Receptor Antagonist

DAYVIGO® Mechanism of Action

DAYVIGO® targets the pathway to regulate wakefulness in the brain.

- A dual orexin receptor antagonist that is thought to treat insomnia by blocking orexin signals that play a role in wakefulness [1]
- Helps patients fall asleep and stay asleep during the night by blocking the orexin pathway to supress the wake drive [1,2]



GABA=gamma aminobutyric acid; OX1R=orexin 1 receptor; OX2R=orein 2 receptor.
*Interaction was defined by in vitro assay when lemborexant (1 or 10 μmol/L) blocked >50% of radioactively labeled ligand specific for the respective receptor target.

References: 1. DAYVIGO (lemborexant) [Prescribing Information]. 2. Rosenberg R, et al. Comparison of lemborexant with placebo and zolpidem tartrate extended release for the treatment of older adults with insomnia disorder: a phase 3 randomized clinical trial. JAMA Netw Open. 2019;2(12):e1918254. 3. Beuckmann CT, et al. In vitro and in silico characterization of lemborexant (E2006), a novel dual orexin receptor antagonist. J Pharmacol Exp Ther. 2017;362(2):287-295.

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DAYVIGO® Safety Studies

SUNRISE 1 and SUNRISE 2 evaluated the safety of DAYVIGO®

SUNRISE 1 (polysomnography)

Primary endpoint: Change from baseline (BL) in latency to persistent sleep vs placebo[1]

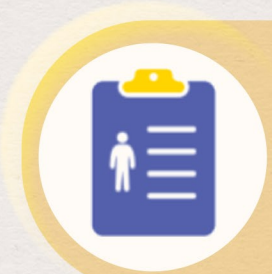
Key secondary endpoints: Change from baseline in sleep efficiency (SE) and wake-after-sleep-onset (WASO) vs placebo[1]

SUNRISE 1

A phase 3 trial which compared the use of DAYVIGO (5mg [n=263]; 10mg [n=269]) to placebo (n=208) or zolpidem (n=263) in males ≥65 and females ≥55 years old.[1]

SUNRISE 2

A phase 3 trial which measured the long-term effectiveness and safety of DAYVIGO (5mg [n=323]; 10mg [n=323]) vs placebo (n=325) in patients ≥18 years old. The study was divided into 2 treatment periods.[2]



SUNRISE 2 (patient diaries)

Primary efficacy endpoint: Mean change from BL in sleep onset latency after 6 months[2]

Key secondary efficacy endpoints: Mean changes from baseline in subjective SE and subjective WASO (sWASO) after 6 months[2]

Abbreviations: BL, baseline; SE, sleep efficiency; WASO, wake-after-sleep-onset; sWASO, subjective WASO.

References: 1. Rosenberg R, et al. JAMA Netw Open. 2019;2:e1918254. 2. Yardley J, et al. Sleep Med. 2021;80:333-342.

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DAYVIGO® demonstrated significant reduction in time to sleep onset.

SUNRISE 1

Significant mean decrease from baseline in LPS observed for both doses of DAYVIGO compared with placebo and zolpidem therapy at Month 1

ENDPOINT: LATENCY TO PERSISTENT SLEEP	PLACEBO n=208	ZOLPIDEM ER 6.25mg n = 263	LEMBOREXANT 5mg n = 263	LEMBOREXANT 10mg n = 266
Results of a global randomized double-blind parallel-group placebo-controlled active-comparator phase 3 study conducted at 67 sites in North America and Europe from May 31, 2016, to January 30, 2018.	-7.9 minutes	-7.5 minutes	-19.5 minutes (p<0.001 vs PBO) (p<0.001 vs ZOL)	-21.5 minutes (p<0.001 vs PBO) (p<0.001 vs ZOL)

SUNRISE 2

DAYVIGO **decreased time to sleep onset over 6 months** vs placebo

ENDPOINT: SUBJECTIVE SLEEP ONSET LATENCY (sSol)	PLACEBO N=325	LEMBOREXANT 5mg N=323	LEMBOREXANT 10mg N=323
Results of a 12-month, global, multicenter, randomized, double-blind, parallel-group phase 3 study comprising a 6-month placebo-controlled period (reported here) followed by a 6-month active-treatment-only period (reported separately).	-11 minutes	-21.81 minutes (p<0.0001)	-28.21 minutes (p<0.0001)

Time to sleep onset measures the amount of time it takes patients to fall asleep

Reference:Kärppä M, Yardley J, Pinner K, Filippov G, Zammit G, Moline M, Perdomo C, Inoue Y, Ishikawa K, Kubota N. Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2. Sleep. 2020 Sep 14;43(9
Rosenberg R, Murphy P, Zammit G, et al. Comparison of Lemborexant With Placebo and Zolpidem Tartrate Extended Release for the Treatment of Older Adults With Insomnia Disorder: A Phase 3 RandomizedClinicalTrial. 2019;2(12)

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DAYVIGO® effectively decreased wake after sleep onset.

SUNRISE 1

Mean decreases from baseline WASO at Month 1 were also significantly larger for both doses of DAYVIGO compared with placebo and zolpidem therapy

ENDPOINT: WAKE AFTER SLEEP ONSET (WASO)	PLACEBO n=208	ZOLPIDEM ER 6.25mg n = 263	LEMBOREXANT 5mg n = 263	LEMBOREXANT 10mg n = 266
Results of a global randomized double-blind parallel-group placebo-controlled active-comparator phase 3 study conducted at 67 sites in North America and Europe from May 31, 2016, to January 30, 2018.	-18.6 minutes	-36.5 minutes (p<0.001 vs PBO)	-43.9 minutes (p<0.001 vs PBO) (p=0.007 vs ZOL)	-46.4 minutes (p<0.001 vs PBO) (p=0.007 vs ZOL)

SUNRISE 2

Statistically significant reductions in sWASO were observed during the first week of treatment and at the end of Month 6

ENDPOINT: SUBJECTIVE WAKE AFTER SLEEP ONSET (sWASO)	PLACEBO N=325	LEMBOREXANT 5mg N=323	LEMBOREXANT 10mg N=323
Results of a 12-month, global, multicenter, randomized, double-blind, parallel-group phase 3 study comprising a 6-month placebo-controlled period (reported here) followed by a 6-month active-treatment-only period (reported separately).	-29.28 minutes	-46.75 minutes (p=0.0005)	-41.95 minutes (p=0.0105)

Wake after Sleep Onset (WASO) measures the amount of time spent awake after initially falling asleep.

Reference:Kärppä M, Yardley J, Pinner K, Filippov G, Zammit G, Moline M, Perdomo C, Inoue Y, Ishikawa K, Kubota N. Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2. Sleep. 2020 Sep 14;43(9
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DAYVIGO® showed clinically significant increase in sleep efficiency.

SUNRISE 1

Mean changes from baseline in SE at Month 1 were also significantly larger for both DAYVIGO 5 mg and 10 mg compared with placebo and zolpidem therapy

ENDPOINT: SLEEP EFFICIENCY (SEF)	PLACEBO n=208	ZOLPIDEM ER 6.25mg n = 263	LEMBOREXANT 5mg n = 263	LEMBOREXANT 10mg n = 266
Results of a global randomized double-blind parallel-group placebo-controlled active-comparator phase 3 study conducted at 67 sites in North America and Europe from May 31, 2016, to January 30, 2018.	5.40%	9.10% (p<0.001 vs PBO)	12.90% (p<0.001 vs PBO) (p=0.007 vs ZOL)	14.10% (p<0.001 vs PBO) (p=0.007 vs ZOL)

SUNRISE 2

Significant increases in sSE in both DAYVIGO 5 mg and 10 mg versus placebo were also observed during the first week of treatment and were sustained over 6 months

ENDPOINT: SUBJECTIVE SLEEP EFFICIENCY (SSE)	PLACEBO N=325	LEMBOREXANT 5mg N=323	LEMBOREXANT 10mg N=323
Results of a 12-month, global, multicenter, randomized, double-blind, parallel-group phase 3 study comprising a 6-month placebo-controlled period (reported here) followed by a 6-month active-treatment-only period (reported separately).	9.64%	14.19% (p=0.0001)	14.31% (p=0.0001)

Sleep Efficiency (SE) is measured by the amount of time spent asleep divided by the total time spent in bed.

Reference:Kärppä M, Yardley J, Pinner K, Filippov G, Zammit G, Moline M, Perdomo C, Inoue Y, Ishikawa K, Kubota N. Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2. Sleep. 2020 Sep 14;43(9
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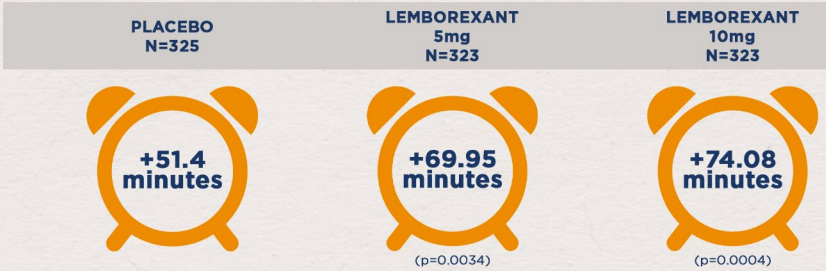
DAYVIGO® remarkably improved sleep maintenance of patients with insomnia.

SUNRISE 2

A significant increase in mean change from baseline in sTST with DAYVIGO 5 mg and 10 mg was seen.

ENDPOINT: CHANGE IN SUBJECTIVE TOTAL SLEEP TIME



Results of a 12-month, global, multicenter, randomized, double-blind, parallel-group phase 3 study comprising a 6-month placebo-controlled period (reported here) followed by a 6-month active-treatment-only period (reported separately).

Subjective Total Sleep Time (sTST) is derived from the minutes spent asleep during their time in bed

Reference:Kärppä M, Yardley J, Pinner K, Filippov G, Zammit G, Moline M, Perdomo C, Inoue Y, Ishikawa K, Kubota N. Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2. Sleep. 2020 Sep 14;43(9
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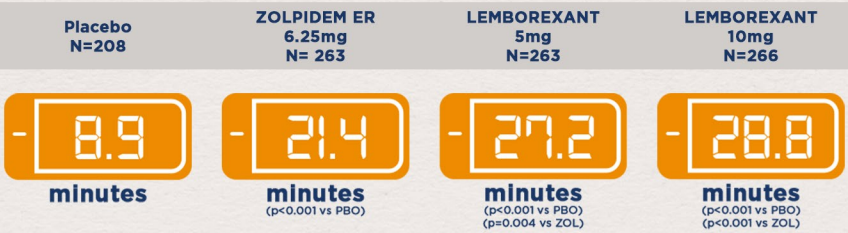
DAYVIGO® showed better improvement in wake after sleep onset 2nd half of the night.

SUNRISE 1

Mean decreases in WASO2H were also significantly larger for both doses of lemborexant therapy compared with placebo and zolpidem ER therapy.

ENDPOINT: WAKE AFTER SLEEP ONSET 2ND HALF OF THE NIGHT (WASO2H)



Results of a 12-month, global, multicenter, randomized, double-blind, parallel-group phase 3 study comprising a 6-month placebo-controlled period (reported here) followed by a 6-month active-treatment-only period (reported separately).

Wake after Sleep Onset 2nd Half of the Night (WASO2H) minutes of wake from 240 minutes after lights off until lights on

Reference:Rosenberg R, Murphy P, Zammit G, et al. Comparison of Lemborexant With Placebo and Zolpidem Tartrate Extended Release for the Treatment of Older Adults With Insomnia Disorder: A Phase 3 RandomizedClinicalTrial. 2019;2(12)

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DAYVIGO® is safe and well tolerated over the study treatment periods.

SUNRISE 1
PSG (Month 1)

Category, n (%)	PLACEBO N=209	ZOLPIDEM ER 6.25mg N=263	LEMBOREXANT 5mg N=266	LEMBOREXANT 10mg N=268
Any treatment-related TEAE	16 (7.7%)	41 (15.6%)	30 (11.3%)	39 (14.6%)
Any TEAE leading to discontinuation of study drug	2 (1.0%)	7 (2.7%)	2 (0.8%)	3 (1.1%)
Headache	13 (6.2%)	14 (5.3%)	17 (6.4%)	13 (4.9%)
Somnolence	4 (1.9%)	4 (1.5%)	11 (4.1%)	19 (7.1%)
Fatigue	2 (1.0%)	2 (0.8%)	6 (2.3%)	9 (3.4%)

SUNRISE 2
PATIENT DIARIES (Month 1)

Category, n (%)	PLACEBO N=319	LEMBOREXANT 5mg N=314	LEMBOREXANT 10mg N=314
Any treatment-related TEAE	44 (13.8%)	78 (24.8%)	91 (29.0%)
Any TEAE leading to discontinuation of study drug	12 (3.8%)	12 (4.1%)	26 (8.3%)
Somnolence	5 (1.6%)	27 (8.6%)	41 (13.1%)
Headache	21 (6.6%)	28 (8.9%)	21 (6.7)
Influenza	15 (4.7%)	15 (4.5%)	16 (5.1%)

Time to sleep onset measures the amount of time it takes patients to fall asleep

Reference:Kärppä M, Yardley J, Pinner K, Filippov G, Zammit G, Moline M, Perdomo C, Inoue Y, Ishikawa K, Kubota N. Long-term efficacy and tolerability of lemborexant compared with placebo in adults with insomnia disorder: results from the phase 3 randomized clinical trial SUNRISE 2. Sleep. 2020 Sep 14;43(9
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DAYVIGO® Dosing and Administration

DAYVIGO® features convenient dosing, given once daily.

RECOMMENDED DOSAGE

- The recommended starting dose of DAYVIGO is 5 mg
- The dose may be increased to the maximum recommended dose of 10 mg, based on clinical response and tolerability
- No need for dose adjustment based on age, race, sex, BMI, and renal impairment
  - Exercise caution when using 10 mg in patients ≥65 years of age
  - Patients with severe renal impairment may experience an increased risk of somnolence
- Avoid alcohol consumption with DAYVIGO

ADMINISTRATION

- DAYVIGO should be taken immediately before going to bed and with at least7 hours remaining before the planned time of awakening
- DAYVIGO should not be taken more than once per night
- Time to sleep onset may be delayed if taken with, or soon after, a meal

Use with CYP3A inhibitors or inducers

- Avoid concomitant use of DAYVIGO with strong or moderate CYP3A inhibitors or inducers
- When co-administered with weak CYP3A inhibitors, the maximum recommended dose of DAYVIGO is 5 mg. no more than once per night

DOSAGE ADJUSTMENT

		Dose adjustment		
		No adjustment	Use 5mg only	Not recommended
Pediatrics (<18 years)				✓
Geriatrics (≥ 65 years)		✓		
Hepatic impairment	Mild	✓		
	Moderate		✓	
	Severe			✓
Renal impairment		✓		
CYP3A inhibitors	Weak		✓	
	Moderate			✓
	Strong			✓
CYP3A inducers				✓
CYP2B6 substrates		Closely monitor the clinical response and may increase dose of those substrates if needed		

Time to sleep onset measures the amount of time it takes patients to fall asleep

Reference:Lemborexant (Dayvigo) Product Insert

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Dayvigo® Special Safety Studies

MORNING

In 2 randomized, placebo- and active- controlled trials in healthy subjects and patients with insomnia ≥55 years of age:

Next-day postural stability

No meaningful differences were observed between DAYVIGO(5 mg or 10 mg) and placebo

Next-day memory

No meaningful differences were observed between DAYVIGO (5 mg or 10 mg) and placebo

Next-morning driving DAYVIGO (5 mg or 10 mg)

did not significantly impair the morning driving performance of healthy volunteers vs those taking placebo

Patients using the DAYVIGO 10 mg dose should be cautioned about the potential for next-morning driving impairment because there is individual variation in sensitivity to DAYVIGO

MIDDLE OF THE NIGHT

In a randomized, placebo- and active- controlled trial in healthy female subjects ≥55 years or male subjects ≥65 years:

Postural stability

Both DAYVIGO doses (5 mg and 10 mg) **impaired balance** (measured by body sway) at 4 hours post dose compared with placebo

Attention and memory

DAYVIGO was associated with **dose-dependent worsening** 4 hours post-dose on measures of attention and memory compared with placebo

Awakening to sound

Neither DAYVIGO dose demonstrated any meaningful differences in patients' ability to awaken to sound compared with placebo

Patients should be cautioned about the potential for middle of the night postural instability as well as attention and memory impairment

Time to sleep onset measures the amount of time it takes patients to fall asleep

Reference:Lemborexant (Dayvigo) Product Insert

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DAYVIGO® is competitively priced that offers safe and effective treatment option for insomnia.

BRAND	GENERIC	REGULAR Rx	DOSE	COST PER TAB
DAYVIGO	**LEMBOREXANT**	**YES**	**5mg/OD**	**₱89.00**
Brand S	Zolpidem	NO	10mg/OD	₱77.75
Brand Z (Generic)	Zolpidem	NO	10mg/OD	₱54.50
Brand D	Midazolam	NO	15mg/OD	₱26.00

Reference: Mercury Drug Price Survey as of July 2022

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1.1 THERAPEUTIC INDICATION

For the treatment of insomnia.

1.2 POSOLOGY AND METHOD OF ADMINISTRATION

1.2.1 Posology
The recommended dose of lemborexant 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 of lemborexant is 10 mg once daily.
Time to sleep onset may be delayed if taken with or soon after a meal.
Patients should be advised not to consume alcohol in combination with lemborexant.
1.2.2 Use with CYP3A Inhibitors
Co-administration with Moderate or Strong CYP3A Inhibitors
Avoid concomitant use of lemborexant 5 or 10 mg with moderate or strong CYP3A inhibitors.
Co-administration with Weak CYP3A Inhibitors
The maximum recommended dose of lemborexant is 5 mg when co-administered with weak CYP3A inhibitors.
1.2.3 Use with CYP3A Inducers
Co-administration with Moderate or Strong CYP3A Inducers
Avoid concomitant use of lemborexant with moderate or strong CYP3A inducers.
1.2.4 Special Populations
1.2.4.1 Renal Impairment
No dose adjustment is required in patients with mild, moderate, or severe renal impairment.
1.2.4.2 Hepatic Impairment
No dose adjustment is required in patients with mild hepatic impairment. The maximum recommended dose of lemborexant is 5 mg in patients with moderate hepatic impairment. Lemborexant is not recommended in patients with severe hepatic impairment.
1.2.4.3 Geriatric Patients
There were no clinically meaningful differences in safety or effectiveness observed between elderly patients (≥65 years) and adult patients at the recommended doses. No dose adjustment is required in geriatric patients. Of the total number of patients treated with lemborexant (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 lemborexant 10 mg was higher (9.8%) compared to 7.7% in patients <65 years. The incidence of somnolence with lemborexant 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.
1.2.4.4 Pediatric Patients
The safety and effectiveness of lemborexant have not been established in pediatric patients (below 18 years of age). Lemborexant is not recommended in pediatric patients.
1.2.4.5 Compromised Respiratory Function
In a study of patients with mild obstructive sleep apnea (apnea-hypopnea index <15 events per hour of sleep) lemborexant did not increase the frequency of apneic events or cause oxygen desaturation. Lemborexant has not been studied in patients with chronic obstructive pulmonary disease or with moderate to severe obstructive sleep apnea.

1.3 METHOD OF ADMINISTRATION

For oral use only.

1.4 CONTRAINDICATIONS

Lemborexant is contraindicated in patients with narcolepsy.

1.5 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

1.5.1 Daytime Impairment
Lemborexant, 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 lemborexant is taken with less than a full night of sleep remaining, or if a higher than the recommended dose is taken. The use of lemborexant with other drugs to treat insomnia is not recommended.

1.6 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

1.6.1 Potential for Other Medicinal Products to Affect Lemborexant
1.6.1.1 Weak, Moderate and Strong CYP3A Inhibitors
Metabolism by CYP3A is the major elimination pathway of lemborexant. Co-administration of lemborexant 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 Cmax by 1.6-fold. Other moderate and strong inhibitors of CYP3A would be expected to have similar effects on plasma levels of lemborexant.
Using a physiologically based pharmacokinetic (PBPK) model, a weak effect is predicted when weak CYP3A inhibitors (e.g., fluoxetine) are co-administered with lemborexant. Avoid concomitant use of lemborexant 5 or 10 mg with moderate or strong CYP3A inhibitors. The maximum recommended dose of lemborexant is 5 mg when co-administered with weak CYP3A inhibitors.
1.6.1.2 Moderate and Strong CYP3A Inducers
Avoid co-administration of lemborexant with moderate or strong CYP3A inducers. Co-administration with a strong CYP3A inducer resulted in a 97% reduction in lemborexant systemic exposure. This may result in a decrease in efficacy.
1.6.1.3 *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.
1.6.1.4 Alcohol
Lemborexant Cmax 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 lemborexant.
1.6.2 Potential for Lemborexant to Affect Other Medicinal Products
1.6.2.1 Clinical Studies with Substrates of CYP3A or CYP2B6
Lemborexant does not induce or inhibit CYP3A4 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 lemborexant.
1.6.2.2 *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.
1.6.2.3 *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.

1.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Although lemborexant at doses of 5 mg and 10 mg did not cause statistically significant impairment in next-morning driving performance in adult or elderly subjects (compared with placebo), driving ability was impaired in some subjects taking 10 mg lemborexant. Patients using the 10 mg dose should be cautioned about the potential for next-morning driving impairment because there is individual variation in sensitivity to lemborexant.

1.8 UNDESIRABLE EFFECTS

1.8.1 Clinical Trial Experience
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.
In controlled efficacy trials (Study 303 and Study 304), 1418 patients were exposed to lemborexant. In Study 303, 434 patients were treated with lemborexant for one year.
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 lemborexant 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 (lemborexant 5 mg 1.1%, lemborexant 10 mg 2.3%, placebo 0.6%).
Most Common Adverse Reactions
In clinical trials of patients with insomnia treated with lemborexant 5 mg or 10 mg, the most common adverse reaction (reported in 5% or more of patients treated with lemborexant and at a higher rate than placebo) was somnolence (lemborexant 5 mg 6.6%, lemborexant 10 mg 10.5%, placebo 1.6%). The majority of the adverse reactions of somnolence were mild in severity.
Table 1 shows the percentage of patients with adverse reactions based on the pooled data (by preferred term and decreasing frequency) from the 6-month controlled treatment period (Study 303) and the 1-month controlled efficacy study (Study 304) where the incidence in the lemborexant 10 mg group was more than placebo.

MedDRA Preferred Term	Placebo (n=528) n (%)	Lemborexant 5 mg (n=580) n (%)	Lemborexant 10 mg (n=582) n (%)
Somnolence	9 (2.0)	38 (7.0)	61 (11.0)
Urinary tract infection	9 (2.0)	7 (1.0)	18 (3.0)
Fatigue	1 (0.2%)	14 (2.0)	12 (2.0)

Other Adverse Reactions
Sleep Paralysis
Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, can occur with the use of lemborexant. In clinical trials, lemborexant was associated with sleep paralysis: lemborexant 5 mg 1.1% or lemborexant 10 mg 1.6% compared to no reports for placebo.
Reporting of suspected adverse reactions
Please contact:
Hi-Eisai Pharmaceutical, Inc.
+63 2 88875837 / +63 2 88875160 / +63 9088672236
Or Report to FDA Philippines: www.fda.gov.ph

1.9 PHARMACODYNAMIC PROPERTIES

1.9.1 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 signaling 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.
1.9.2 Pharmacodynamics
1.9.2.1 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 analyzed 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.

1.10 PHARMACOKINETIC PROPERTIES

1.10.1 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 (tmax) 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 Cmax.
Ingestion of lemborexant with a high-fat meal resulted in a slight decrease in the rate of absorption as demonstrated by 23% decrease in Cmax and delay in tmax of 2 hours and 18% increase in total exposure AUC.
Time to sleep onset may be delayed if taken with or soon after a meal.
1.10.2 Distribution
The volume of distribution of lemborexant is 1970 L. Protein binding of lemborexant in clinical samples is approximately 94%. The blood to plasma concentration ratio of lemborexant is 0.65.
In vitro binding of lemborexant and its major circulating metabolite, M10 (the N-oxide of lemborexant) to human plasma proteins ranged from 87.4% to 88.7% and 91.5% to 92.0%, respectively, at concentrations of 100 to 1000 ng/mL. At these concentrations in vitro, lemborexant was bound primarily to human serum albumin, low-density lipoprotein, and high-density lipoprotein. In vitro blood to plasma concentration ratios of lemborexant and M10 in humans were 0.610 to 0.656 and 0.562 to 0.616, respectively, at concentrations of 100 to 1000 ng/mL.
1.10.3 Metabolism
Lemborexant is primarily metabolized 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 pharmacologic activity of lemborexant is thought to be minimal.
1.10.4 Elimination
The primary route of elimination is through the feces, with 57.4% of radiolabeled dose recovered in the feces 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.
1.10.5 Special Populations
1.10.5.1 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.
1.10.5.2 Geriatric Patients
Based on a population pharmacokinetic analysis in patients receiving 5 or 10 mg lemborexant once daily, apparent clearance was 26% lower in elderly (>65 years of age). However, this effect was not clinically relevant.
1.10.5.3 Pediatric Patients
No studies have been conducted to investigate the pharmacokinetics of lemborexant in pediatric patients.
1.10.5.4 Patients with Renal Impairment
Severe renal impairment (urinary creatinine clearance ≤30 mL/min/1.73m2) increased lemborexant exposure (AUC) 1.5-fold but had no effect on Cmax. No dose adjustment is required in patients with renal impairment.
1.10.5.5 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 Cmax by 1.5-fold. Terminal half-life was only increased in patients with moderate hepatic impairment (Child-Pugh class B). No relationship between these findings and hepatic function was observed.

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADMINISTRATIVE DATA
MARKETING AUTHORIZATION HOLDER
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MARKETING AUTHORIZATION NUMBER
DR-XY47690
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Mercury Drug Price

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