

EISAI TO LAUNCH IN-HOUSE DEVELOPED NEW ANTI-INSOMNIA DRUG DAYVIGO® (LEMBOREXANT) WITH INDICATION FOR INSOMNIA IN JAPAN

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, “Eisai”) announced today that it has launched its in-house-discovered and developed orexin receptor antagonist DAYVIGO® 2.5 mg, 5 mg, 10 mg tablets (lemborexant) for treatment of insomnia in Japan on July 6, 2020. Eisai received marketing and manufacturing approval for this formulation on January 23, 2020, and the product was added to Japan’s National health Insurance drug price list on April 22, 2020.



DAYVIGO is a dual orexin receptor antagonist that inhibits orexin neurotransmission regulating sleep-wake rhythm by binding competitively to the two subtypes of orexin receptors (OX1R and OX2R). DAYVIGO acts on the orexin neurotransmitter system and is believed to facilitate sleep onset, sleep maintenance, and wake by regulating sleep-wake rhythm.

The approval of DAYVIGO in Japan is based on findings from two pivotal Phase III studies^{1,2} (SUNRISE 1 and SUNRISE 2) in adult patients with insomnia, as well as evaluation of residual effects including middle of the night waking, next morning postural stability (falling prediction indicator), and memory through Studies 106³ and 108⁴.

The SUNRISE 1¹ clinical trial conducted in North America and Europe utilized objective assessment with overnight measurement through polysomnography, and confirmed statistically significant shortening or improvement of sleep onset latency (primary objective) as well as sleep efficiency and wake after sleep onset (secondary objectives) with DAYVIGO compared to tartrate-sustained-release drug zolpidem (6.25 mg, not yet approved in Japan) and placebo. The SUNRISE 2² clinical trial, conducted globally including in Japan, evaluated patients subjectively through sleep diaries and confirmed statistically significant improvement in sleep onset latency (primary objective) as well as subjective sleep efficiency and subjective wake after sleep onset (secondary objectives) compared to placebo. Main side effects of DAYVIGO as observed in the two trials were somnolence, headache, dizziness, and fatigue. Analyses in both studies suggested DAYVIGO was not associated with rebound insomnia, and there was no evidence of withdrawal effects following treatment discontinuation, suggesting it does not produce physical dependence in those taking it for up to one year.

In a special safety study (Study 106)³, DAYVIGO at 5 mg and 10 mg doses did not cause statistically significant impairment in next morning driving performance in healthy adult or elderly subjects (compared with placebo). Additional special safety studies (Study 108)⁴ evaluated middle-of-the-night safety, next morning postural stability and memory. The effects of DAYVIGO on next day postural stability and memory were evaluated in two randomized, placebo and active-controlled trials. There were no meaningful differences between DAYVIGO and placebo on next-day postural stability or memory at either dose. While there is a need for caution regarding the potential for middle-of-the-night postural instability as well as attention and memory impairment, no problem-signifying degradation was observed between DAYVIGO- and placebo-administered groups.

In June 2020, DAYVIGO was launched in the U.S. for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. In addition, Eisai submitted a new drug application seeking approval of DAYVIGO in Canada and Australia.

Insomnia is characterized by difficulty falling asleep, staying asleep or both, despite an adequate opportunity to sleep, that can lead to daytime consequences, such as fatigue, difficulty concentrating and irritability.^{5,6} Insomnia is one of the most common sleep-wake disorders. Approximately 30% of adults worldwide have symptoms of insomnia.^{7,8} In particular, older adults tend to have a higher prevalence rate with many experiencing insomnia symptoms for months to years. As a result, insomnia causes various social losses, such as long absences and reduced productivity. It can increase the risk of falling in older adults.⁹

Through the launch of DAYVIGO, Eisai will continue to prioritize the provision of appropriate usage and safety information. By providing DAYVIGO as a new option for the treatment of insomnia, Eisai aims for contribution to restoration of daytime function and recovery for patients with insomnia by delivering an active daytime life through fast sleep onset and good quality sleep.

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[Notes to editors]

1. Product Information

1) Product name

DAYVIGO® tablets 2.5 mg, DAYVIGO® tablets 5 mg, DAYVIGO® tablets 10 mg

2) Generic name

Lemborexant

3) Indications

Insomnia

4) Dosage and Administration

The usual adult dosage is 5 mg of lemborexant for oral use at bedtime. The dosage may be adjusted based on the patient's symptoms, but the maximum dosage must not exceed 10 mg per day.

5) Price

DAYVIGO tablets 2.5 mg 57.30 JPY/tablet

DAYVIGO tablets 5 mg 90.80 JPY/tablet

DAYVIGO tablets 10 mg 136.20 JPY/tablet

6) Packaging

DAYVIGO tablets 2.5 mg (10 tablet PTP sheet X 10), 100 tablets

DAYVIGO tablets 5 mg (10 tablet PTP sheet X 10), 100 tablets

DAYVIGO tablets 10 mg (10 tablet PTP sheet X 10), 100 tablets

2. About DAYVIGO (Lemborexant)

DAYVIGO is Eisai's in-house discovered and developed small molecule that binds to orexin receptors, OX1R and OX2R, and acts as a competitive antagonist (IC₅₀ values of 6.1 nM and 2.6 nM, respectively). The mechanism of action of DAYVIGO in the treatment of insomnia is presumed to be through antagonism of orexin receptors. The orexin neuropeptide signaling system plays a role in wakefulness. Blocking the binding of wake-promoting neuropeptides orexin to receptors OX1R and OX2R is thought to suppress wake drive (K_i values of 8.1 nM and 0.48 nM, respectively). Higher affinity and faster on/off receptor kinetics of DAYVIGO to orexin receptor 2, which also suppresses non-REM sleep, indicates its potential to facilitate non-sedative onset and maintenance of sleep.

Based on clinical study results, the effects of DAYVIGO are suggested not only for primary insomnia, but also for insomnia associated with other diseases, such as depression (SUNRISE 2).

In addition to the indication of insomnia, a Phase II clinical study of DAYVIGO in patients with Irregular Sleep Wake Rhythm Disorder (ISWRD) associated with mild-to-moderate Alzheimer's dementia is underway.

3. About Sleep-Wake Disorders and Insomnia

Sleep-wake disorders consist of disease categories such as insomnia, ISWRD, hypersomnia and breathing-related sleep disorders. Among the sleep-wake disorders, insomnia is the most common with persistent insomnia symptoms experienced by approximately 30 percent of the adult population worldwide.^{7,8} Insomnia disorder is characterized by difficulty falling asleep, staying asleep or both, despite an adequate opportunity to sleep. It can lead to daytime consequences, such as fatigue, difficulty concentrating and irritability.^{5,6}

Good quality sleep is essential for good health, including brain health.¹⁰ Studies suggest an optimal sleep duration between seven and eight hours.¹¹ Poor sleep is associated with a wide range of health consequences, including an increased risk of hypertension, accidental injury, diabetes, obesity, depression, heart attack, stroke, dementia and adverse effects on mood and behavior.^{5,12}

Women are 1.4 times more likely than men to suffer from insomnia.¹³ Older adults also have higher prevalence of insomnia as aging is often accompanied by changes in sleep patterns, including disrupted sleep, frequent waking, and early waking, that can lead to less sleep time.¹⁴

4. About SUNRISE 1 (Study 304)¹

SUNRISE 1 is a multicenter, randomized, double-blind, placebo-controlled, active comparator, parallel-group Phase III study of the efficacy and safety of lemborexant in 1,006 patients 55 years and older (45% of all patients were aged 65 years and older) with insomnia disorder conducted in North America and Europe. SUNRISE 1 included a pre-randomization phase of up to 35 days (including a two-week placebo run-in period) and a randomization phase comprised of a 30-day treatment period and a two-week period without treatment prior to the end-of-study-visit. In this study, patients were administered placebo or one of three treatment regimens (lemborexant 5 mg, lemborexant 10 mg, zolpidem ER 6.25 mg).

The primary objective for SUNRISE 1 was to demonstrate using polysomnography that lemborexant at either the 5 mg or 10 mg dose is superior to placebo on objective sleep onset, as measured by latency to persistent sleep after the last two nights of one month of treatment. Key secondary endpoints included change from baseline in sleep efficiency for both lemborexant doses compared to placebo, wake after sleep onset (WASO) for both lemborexant doses compared to placebo, and WASO in the second half of the night (WASO2H) for both lemborexant doses compared to zolpidem ER, after one month of treatment, measured objectively by polysomnography.

The results of the study showed that lemborexant had statistically significant improvement compared to zolpidem ER 6.25 mg and placebo in sleep parameters evaluated in primary and key secondary endpoints. The common adverse events (AEs) in the lemborexant arms were headache and somnolence.

5. About SUNRISE 2 (Study 303)²

SUNRISE 2 is a 12-month multicenter, global (Japan, North America, South America, Europe, Asia, and Oceania), randomized, placebo-controlled, double-blind, parallel group Phase III study of 949 male or female adult participants (18 to 88 years of age) with insomnia disorder. SUNRISE 2 included a pre-randomization phase of up to 35 days (including a two-week placebo run-in period) and a randomization phase comprised of a six-month placebo-controlled treatment period, a six-month period of only active treatment, and a two-week period without treatment prior to the end-of-study-visit. Lemborexant 5 mg, 10 mg or matching placebo was taken orally in tablet form at home each night immediately before the patient intended to try to sleep for the first six months of study. Patients who received placebo during the first six-month period were administered lemborexant 5 mg or 10 mg for the second six-month period. Patients who received active treatment during the first period continued on the treatment to which they were originally randomized.

The primary outcome measure was mean change from baseline in subjective sleep onset latency after six months of placebo-controlled treatment. Key secondary outcome measures were mean change from baseline in subjective sleep efficiency and subjective wake after sleep onset after six months of placebo-controlled treatment.

From the results, the primary endpoint and all secondary endpoints for efficacy were achieved for lemborexant arms, and statistically significant improvements in sleep onset and sleep maintenance were confirmed for lemborexant arms compared to placebo during the six-month treatment period. The common AEs in the lemborexant arms were somnolence, nasopharyngitis, headache and influenza.

6. About Study 106³

Study 106 was a randomized, double-blind, placebo- and active-controlled, four period, crossover Phase I study to evaluate the effect of lemborexant in 48 healthy adults and elderly volunteers (23 to 78 years of age, mean: 58.5 years old) to evaluate on-road driving performance. Volunteers (65 years and older: 24, 23 to 64 years old: 24) were treated at bedtime with two out of three dose levels of lemborexant (2.5, 5 or 10 mg) and placebo for eight consecutive days. Zopiclone 7.5 mg as an active control was administered on days one and eight only, with placebo given for the six days in between. The primary endpoint was to evaluate change of standard deviation of lateral position (SDLP) during an on-road driving test conducted after the first (in the morning of Day 2) and last day (in the morning of Day 9) of treatment administration after 9-hour dose.

In the on-road test, the volunteers drove a specially instrumented vehicle for about one hour over 100km (approximately 60 miles) primary highway circuit, accompanied by a licensed driving instructor. The task was to drive

with a steady lateral position between the delineated boundaries of the slower traffic lane, while maintaining a constant speed of 95km/h. Although lemborexant at doses of 5 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. Decreased vehicle driving ability was shown in some subjects taking 10 mg of lemborexant, and the effects of this drug could extend to next morning after administration and drowsiness, decreased attention, concentration, reflex motor capacity, etc. may occur. Therefore, it is necessary to be careful not to engage in dangerous machinery operations such as driving a car.

7. About Study 108⁴

Study 108 was a randomized, double-blind, four period crossover Phase I study to evaluate the effect of lemborexant on postural stability, auditory awakening threshold, and cognitive performance in 56 healthy volunteers 55 years and older. Participants were treated at bedtime with a single dose of placebo, lemborexant 5 mg, lemborexant 10 mg, or zolpidem ER 6.25 mg. The primary endpoint assessed postural stability when awakened by an alarm approximately four hours after administration of lemborexant compared to zolpidem ER, as measured by stabilometer.

While there was a statistically significant increase in body sway for both doses of lemborexant compared with placebo, Zolpidem ER increased body sway at a magnitude almost three times more than lemborexant. This increase with zolpidem was three times that, which is associated with a blood alcohol content (BAC 0.05 percent) near the legal driving limit.

The next morning, shortly after the end of eight hours in bed, unlike zolpidem ER, neither dose of lemborexant had statistically significant residual effects on this measure of postural stability as compared to placebo.

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