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Eisai Co., Ltd.

U.S. FDA APPROVES EISAI'S DAYVIGO™ (LEMBOREXANT) FOR TREATMENT OF INSOMNIA IN ADULT PATIENTS

OREXIN RECEPTOR ANTAGONIST PROVEN EFFECTIVE FOR BOTH SLEEP ONSET AND SLEEP MAINTENANCE IN CLINICAL DEVELOPMENT PROGRAM OF MORE THAN 2,000 PATIENTS

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") today announced that the U.S. Food and Drug Administration (FDA) approved the new drug application for its in-house discovered and developed orexin receptor antagonist DAYVIGO™ (lemborexant). DAYVIGO was approved for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance in adults[1]. In the United States, DAYVIGO will be commercially available in 5 mg and 10 mg tablets following scheduling by the U.S. Drug Enforcement Administration (DEA), which is expected to occur within 90 days.

The mechanism of action of lemborexant in the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance 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 A and orexin B to orexin receptors OX1R and OX2R is thought to suppress wake drive. Lemborexant binds to orexin receptors OX1R and OX2R and acts as a competitive antagonist with stronger inhibition effect to OX2R*.

The approval was based on the results of a clinical development program that included two pivotal Phase III studies (SUNRISE 2 and SUNRISE 1), which evaluated DAYVIGO versus comparators for up to one month and DAYVIGO versus placebo for six-months, respectively, in a total of about 2,000 adult patients with insomnia. From these studies results, DAYVIGO demonstrated statistically significant superiorities on sleep onset and sleep maintenance compared to placebo in both subjective and objective evaluations.

Across SUNRISE 2 and SUNRISE 1, DAYVIGO was not associated with rebound insomnia following treatment discontinuation, and there was no evidence of withdrawal effects following DAYVIGO discontinuation at either dose. In addition, the development program included multiple safety studies evaluating effects on postural stability, cognition, driving performance and respiratory safety.

- SUNRISE 2 was a long-term (six month), randomized, double-blind, placebo-controlled, multi-center, trial in adult patients age 18 or older who met DSM-5** criteria for insomnia disorder. Patients were randomized 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 six months for patient-reported (subjective) sleep onset latency (sSOL), defined as the estimated minutes from the time that the subject attempted to sleep until falling asleep. Pre-specified secondary efficacy endpoints were change from baseline to end of treatment at six months for patient reported sleep efficiency (sSE; defined as the proportion of time spent asleep during time in bed) and subjective sleep onset and sleep maintenance (sWASO; defined as the minutes of wake from the onset of persistent sleep until lights on). The primary and pre-specified secondary efficacy endpoints were

measured using a Sleep Diary. In SUNRISE 2, DAYVIGO 5 mg and 10 mg demonstrated statistically significant superiority on the primary efficacy measure, sSOL, compared to placebo. DAYVIGO 5 mg and 10 mg also showed statistically significant superiority in sSE and sWASO.[1]

- SUNRISE 1 was a short-term (one month), randomized, double-blind, placebo- and active-controlled, multi-center, parallel-group clinical trial in adult female subjects age 55 and older and male subjects 65 years and older who met DSM-5 criteria for insomnia disorder. Patients were randomized to placebo (n=208), DAYVIGO 5 mg (n=266) or 10 mg (n=269) or active comparator (n=263) once nightly. The primary efficacy endpoint was the mean change in latency to persistent sleep (LPS; defined as the number of minutes from lights off to the first 10 consecutive minutes of non-wakefulness) from baseline to end of treatment (day 29/30), as measured by overnight polysomnography (PSG) monitoring. The pre-specified secondary efficacy endpoints in SUNRISE 1 were the mean change from baseline to end of treatment (day 29/30) in sleep efficiency (SE) and wake after sleep onset (WASO) measured by PSG. In SUNRISE 1, DAYVIGO 5 mg and 10 mg demonstrated statistically significant superiority on the primary efficacy measure, LPS, compared to placebo. DAYVIGO 5 mg and 10 mg demonstrated statistically significant improvement in SE and WASO compared to placebo.[1]

The most common adverse reaction (reported in 5% or more of patients treated with DAYVIGO and at least twice the rate of placebo) in SUNRISE 2 (the first 30 days) and SUNRISE 1 was somnolence (DAYVIGO 10 mg, 10%; DAYVIGO 5 mg, 7%; placebo, 1%).

In addition to these pivotal trials, Eisai conducted a number of studies to further evaluate the safety of DAYVIGO, including a study that assessed the effect of DAYVIGO on postural stability and cognitive performance and a next-morning driving study.

- Middle of the Night Safety (Study 108): The effect of DAYVIGO on middle of the night safety was evaluated in a randomized, placebo- and active-controlled trial in healthy female subjects ≥ age 55 or male subjects ≥ age 65. Postural stability, the ability to awaken in response to a sound stimulus, and attention and memory were assessed following a scheduled awakening four hours after the start of the eight-hour time in bed. Nighttime dosing of DAYVIGO 5 and 10 mg resulted in impairment of balance (measured by body sway area) at four hours as compared to placebo. There were no meaningful differences between DAYVIGO (5 or 10 mg) and placebo on ability to awaken to sound. DAYVIGO was associated with dose-dependent worsening on measures of attention and memory as compared to placebo.[1]
- Effects on Next-day Postural Stability and Attention and Memory (SUNRISE1 and Study 108): The effects of DAYVIGO on next day postural stability and attention and memory were evaluated in two randomized, placebo- and active-controlled trials in healthy subjects and insomnia patients age 55 and older. There were no meaningful differences between DAYVIGO (5 or 10 mg) and placebo on next-day postural stability, or memory compared to placebo. [1]
- Effects on Driving (Study 106): A randomized, double-blind, placebo- and active-controlled, four-period crossover study evaluated the effects of nighttime administration of DAYVIGO on next-morning driving performance approximately nine hours after dosing in 24 healthy elderly subjects (≥65 years old, median age 67 years) and 24 adult subjects (median age 49 years). Although DAYVIGO 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 DAYVIGO.

“Insomnia disorder is a chronic condition that has a variety of potential negative impacts and long-term

consequences for health and well-being,"[2] said Russell Rosenberg, PhD, D.ABSM, a principal investigator in the DAYVIGO clinical studies and former Chairman of the Board of the National Sleep Foundation. "The clinical trials provide evidence that DAYVIGO may improve patients' ability to fall asleep and stay asleep."

"We believe the approval of DAYVIGO is particularly exciting because it is the first FDA-approved medication to report safety data over a 12-month period along with sleep onset and sleep maintenance efficacy data over a six-month period in a pivotal clinical study," said Lynn Kramer, MD, Chief Clinical Officer, Neurology Business Group, Eisai. "We look forward to making this new therapeutic option available to the millions of patients who suffer with insomnia.

Eisai has submitted new drug applications seeking approval of this agent for use in the treatment of insomnia in Japan (March 2019) and Canada (August 2019).

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.[2,9] Insomnia is one of the most common sleep-wake disorders with high prevalence. Approximately 30% of adults worldwide have symptoms of insomnia,[7,8] and many of them remain months to years. As a result, insomnia causes various social losses such as long absences and reduced productivity.

With DAYVIGO and through its research and development efforts focusing on orexin biology, Eisai aspires to improve the lives of patients suffering from sleep disorders.

*Lemborexant binds to orexin receptors, OX1R and OX2R and acts as a competitive antagonist (IC_{50} values of 6.1 nM and 2.6 nM, respectively). When activated, the role of OX1R is to suppress REM sleep, and the role of OX2R is to suppress both non-REM sleep and REM sleep. Lemborexant enables sleep by preventing activation of OX1R and OX2R.
**DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association)

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[Notes to editors]

1. About Lemborexant

Lemborexant 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 lemborexant 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 A and orexin B to receptors OX1R and OX2R is thought to suppress wake drive.
As a result of clinical studies, the effect of lemborexant are suggested not only for primary insomnia but also for insomnia which is associated with other diseases, such as depression, (SUNRISE-1 and SUNRISE-2).
In addition to the indication of insomnia, a Phase II clinical study of lemborexant in patients with ISWRD associated with mild to moderate Alzheimer's dementia is underway.

2. 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, that can lead to daytime consequences such as fatigue, difficulty concentrating and irritability.[2,9]

Good quality sleep is essential for good health including brain health,[11] and studies suggest an optimal sleep duration between seven and eight hours.[12] 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, as well as adverse effects on mood and behavior.[2,10]

Women are 1.4 times more likely than men to suffer from insomnia.[13] Older adults also have higher prevalence of insomnia; 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]

3. SUNRISE 2 (Study 303)[4]

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.

4. SUNRISE 1 (Study 304)[3]

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 DAYVIGO arms were headache and somnolence.

5. About Study 106[5]

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 58 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.

6. About Study 108[6]

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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