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Eisai Co., Ltd.

EISAI LAUNCHES NEW INSOMNIA DRUG DAYVIGO™ (LEMBOREXANT) CIV IN THE UNITED STATES AS A TREATMENT OPTION FOR ADULTS WITH INSOMNIA

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that its U.S. subsidiary Eisai Inc. has launched its in-house discovered orexin receptor antagonist DAYVIGO™ (lemborexant) CIV for the treatment of adults with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance in the U.S. on June 1, 2020.

Discovered at Eisai's Tsukuba Research Laboratories and developed in-house, DAYVIGO is a small-molecule compound. The mechanism of action in the treatment of insomnia is presumed to be through antagonism of orexin receptors[1]. The orexin neuropeptide signaling system plays a role in wakefulness[1]. 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 (IC50 values of 6.1 nM and 2.6 nM, respectively).

DAYVIGO was approved in the U.S. by the U.S. Food and Drug Administration (FDA) based on findings from the lemborexant clinical development program, which included two pivotal Phase 3 studies[2] (SUNRISE 1 and SUNRISE 2) in nearly 2,000 adult patients with insomnia.

SUNRISE 1 was a 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 (the Diagnostic and Statistical Manual of Mental Disorders – 5th edition) criteria for insomnia disorder. 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 secondary efficacy endpoints in SUNRISE 1 were the mean change from baseline to end of treatment (day 29/30) in sleep efficiency (SEF) 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 and active-controlled.

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. 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 sleep onset. Pre-specified secondary efficacy endpoints for sleep maintenance were change from baseline to end of treatment at six months for patient reported sleep efficiency (sSEF; defined as the proportion of time spent asleep per time in bed) and wake after sleep onset (sWASO; defined as the minutes of wake from the onset of sleep until wake time). The pre-specified primary and

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 sSEF and sWASO.[1]

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. DAYVIGO is the first FDA-approved insomnia medication with safety data over a 12-month treatment period and with sleep onset and sleep maintenance efficacy data over a six-month treatment period in a pivotal clinical study.

The most common adverse reaction (reported in 5% or more of patients treated with DAYVIGO and at least twice the rate of placebo) in the SUNRISE1 and SUNRISE2 (SUNRISE2 was initiated 30 days after first dosing) studies was somnolence (DAYVIGO 10 mg, 10%; DAYVIGO 5 mg, 7%; placebo, 1%).

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). Impairment was seen in some people taking the 10 mg dose. 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. 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 in healthy subjects and insomnia patients age 55 and older. There were no meaningful differences between DAYVIGO and placebo on next-day postural stability or memory at either dose. Patients should be cautioned about the potential for middle-of-the-night postural instability as well as attention and memory impairment.

DAYVIGO (5 mg, 10 mg tablets) received approval from the U.S. FDA in December 2019, and was designated as a Schedule IV controlled substance by the U.S. Drug Enforcement Administration (DEA) in April 2020. According to this Schedule IV designation, individuals with a history of abuse or addiction to alcohol or other drugs may be at an increased risk for abuse and addiction to DAYVIGO and such patients should be followed carefully. Eisai received manufacturing and marketing approval for DAYVIGO as an insomnia treatment in Japan in January 2020, and was included in Japan's National Health Insurance Drug Price List in April 2020. It is being prepared for launch in Japan. Eisai has also submitted a new drug application seeking approval of this agent for use in the treatment of insomnia in Canada in August 2019.

Insomnia is characterized by difficulty falling asleep, staying asleep, or both, despite an adequate opportunity to sleep[5, 6]. 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 persist for months to years.

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

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[Notes to editors]

1. About DAYVIGO™ (Lemborexant)

Lemborexant is Eisai's in-house discovered and developed small molecule that binds to orexin receptors, OX1R and OX2R (IC50 values of 6.1 nM and 2.6 nM, respectively) and acts as a competitive antagonist with stronger inhibition effect to OX2R. In individuals with insomnia, it is possible that orexin signaling regulating wakefulness is not functioning normally.

The orexin neuropeptide signaling system plays a role in wakefulness.[2] Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress wake drive. DAYVIGO is being prepared for launch in Japan. Eisai has also submitted a new drug application seeking approval of this agent for use in the treatment of insomnia in Canada in August 2019.

For further information on DAYVIGO in the United States, including Important Safety Information (ISI), please visit the DAYVIGO website (DAYVIGO.com).

2. About Sleep-Wake Disorders and Insomnia

Sleep-wake disorders consist of disease categories such as insomnia, Irregular Sleep-Wake Rhythm Disorder (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.[5,6]

Diagnostic criteria in the U.S. for insomnia disorder include if the sleep disturbance causes clinically significant distress or impairment in social, occupational, educational, academic, behavioral or other important areas of functioning, occurs at least three nights per week and is present for at least three months.

Sleeping well is essential for good health[9], and studies suggest an optimal sleep duration between seven and eight hours.[10] Poor sleep is associated with a wide range of health consequences.[5,12]

Women are 1.4 times more likely than men to suffer from insomnia.[11] 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.[12]

3. About SUNRISE 1 (Study 304)[2]

SUNRISE 1 is a one-month 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 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 from baseline to end of treatment at Days 29/30 in latency to persistent sleep (LPS; the number of minutes from lights off to the first 10 consecutive minutes of non-wakefulness). Secondary efficacy endpoints were the mean change from baseline to end of treatment at Days 29/30 in sleep efficiency (SEF) and wake after sleep onset (WASO). These endpoints were measured by overnight polysomnography monitoring.

4. About SUNRISE 2 (Study 303)[2]

SUNRISE 2 is a six-month placebo-controlled treatment trial with a 6-month parallel-group extension period including 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 subjective sleep onset latency (sSOL; the estimated minutes from the time that the patient attempted to sleep until sleep onset). Secondary efficacy endpoints were mean change from baseline to end of treatment at six months subjective sleep efficiency (sSEF; the proportion of time spent asleep per time in bed) and wake after sleep onset (sWASO; the minutes of wake from the onset of sleep until wake

time). These endpoints were measured by sleep diary.

5. About Study 106[3]

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 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.

6. About Study 108[4]

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 active control. There was a statistically significant increase in body sway for both doses of lemborexant compared with placebo. The next morning, shortly after the end of eight hours in bed neither dose of lemborexant had statistically significant residual effects on this measure of postural stability as compared to placebo.

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