NEW DRUGS

Lemborexant

Approved indication: insomnia

Dayvigo (Eisai)
5 mg and 10 mg film-coated tablets

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Lemborexant is a dual orexin receptor antagonist indicated for the treatment of insomnia, characterised by difficulties with sleep onset or sleep maintenance. Orexins are neuropeptides involved in regulating sleep and arousal by promoting wakefulness. Lemborexant blocks the binding of orexins A and B to their receptors 1 and 2 thereby reducing wakefulness and promoting sleep. Suvorexant is the other orexin receptor antagonist marketed in Australia for insomnia.

A single dose of lemborexant is taken a few minutes before going to bed, with at least seven hours remaining before the planned time of awakening. Lemborexant is rapidly absorbed with a time to peak concentration of 1–3 hours. The time to sleep onset may increase if lemborexant is taken with or soon after a meal. Lemborexant is mainly metabolised by cytochrome P450 (CYP) 3A4 with most of the metabolites being excreted in the faeces. The concomitant use of moderate or strong CYP3A inhibitors or inducers should be avoided. The effective half-life is 17 hours for lemborexant 5 mg and is 19 hours for lemborexant 10 mg.

Lemborexant is not recommended for patients with severe hepatic impairment. However, severe renal impairment has little effect on drug concentrations. Lemborexant has not been studied in patients with chronic obstructive pulmonary disease or moderate to severe obstructive sleep apnoea.

In a pivotal phase III trial of lemborexant, 1006 participants 55 years and older with insomnia received lemborexant, 5 mg or 10 mg, or zolpidem extended-release 6.25 mg or a placebo for one month at bedtime. The effect of treatment was assessed using polysomnography. Before treatment, the time to persistent sleep was approximately 45 minutes. After four weeks, this reduced to 25.8 minutes with lemborexant 5 mg, 22.8 minutes with lemborexant 10 mg, 37.1 minutes with zolpidem and 36 minutes with placebo. The sleep efficiency increased by 13–14% corresponding to an increase in the total sleep time of at least 60 minutes with lemborexant.[1]

Another phase III trial of lemborexant analysed 949 participants 18 years and older with insomnia who received placebo or lemborexant, 5 mg or 10 mg, for six months, followed by six months of lemborexant 5 mg or 10 mg. Patients who had received placebo in the first six months were re-randomised to lemborexant 5 mg or 10 mg. The patients maintained daily sleep diaries. After six months, participants taking lemborexant were falling asleep 22–28 minutes faster and sleeping for 70–74 minutes longer compared with baseline.[2] These results were maintained after 12 months of treatment. There were no reports of rebound insomnia or withdrawal following treatment discontinuation after 12 months.[3]

There were no statistically significant differences in adverse events across the placebo and lemborexant groups in the six-month analysis.[2] Adverse events caused discontinuation in 3.8% of the placebo group, 4.1% of the lemborexant 5 mg group, and 8.3% of the lemborexant 10 mg group. The most common adverse event was somnolence, which was more common in patients 65 years and older who received the 10 mg dose (2.3% vs 1.1% for lemborexant 5 mg vs 0.6% for placebo). Other less common adverse events included headache and fatigue.[2]

The incidence of suicidal ideation increases after taking lemborexant (0.3% for lemborexant 10 mg, 0.4% for lemborexant 5 mg, and 0.2% for placebo). Alcohol and other drugs that depress the central nervous system should be avoided. The safety of lemborexant in children and pregnant women is unknown. Lemborexant is contraindicated in narcolepsy.

A company-funded network meta-analysis of 45 studies compared lemborexant with 15 other insomnia treatments. Although the confidence intervals overlapped, patients receiving lemborexant were found to have the longest total sleep time, shortest time to persistent sleep and highest sleep efficiency. Treatment outcomes were similar in older adults. The safety profile, severe adverse events and rates of withdrawals due to adverse events were similar for lemborexant and all the other treatments.[4]

Lemborexant is effective and well tolerated for the treatment of insomnia. The lowest number of tablets feasible should be prescribed for the shortest possible time. To minimise the risk of discontinuation due to adverse events such as somnolence, the starting dose of lemborexant should be 5 mg.

[T] manufacturer provided the product information

REFERENCES

1. Rosenburg R, Murphy P, Zammit G, Mayleben D, Kumar D, Dhadda S, 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:e1918254. https://doi.org/10.1001/jamanetworkopen.2019.18254
2. Kärppä M, Yardley J, Pinner K, Filippov G, Zammit G, Moline M, et al. 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;43:zsaa123. https://doi.org/10.1093/sleep/zsaa123

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

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3. Yardley J, Kärppä M, Inoue Y, Pinner K, Perdomo C, Ishikawa K, et al. Long-term effectiveness and safety of lemborexant in adults with insomnia disorder: results from a phase 3 randomized clinical trial. Sleep Med 2021;80:333-42. https://doi.org/10.1016/j.sleep.2021.01.048
4. McElroy H, O'Leary B, Adena M, Campbell R, Monfared AAT, Meier G. Comparative efficacy of lemborexant and other insomnia treatments: a network meta-analysis. J Manag Care Spec Pharm 2021;27:1296-308. https://doi.org/10.18553/jmcp.2021.21011

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA.