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Suvorexant

Approved indication: insomnia
Belsomra (Merck Sharp and Dohme)
15 mg and 20 mg tablets

Australian Medicines Handbook section 18.4

There are different patterns of insomnia, such as a delayed onset of sleep and difficulty maintaining sleep. Orexins are neuropeptides which are involved in the regulation of sleep and arousal. Orexins A and B promote wakefulness. Blocking their receptors should therefore reduce wakefulness and promote sleep. Suvorexant is the first orexin receptor antagonist to be marketed in Australia.

The drug is taken within 30 minutes of bedtime. This should be at least seven hours before the patient plans to get up again. The maximum drug concentration is reached in two hours. Suvorexant is metabolised with most of the metabolites being excreted in the faeces. Its half-life is approximately 12 hours.

Suvorexant is not recommended for patients with severe liver impairment. However, severe renal impairment has little effect on drug concentrations.

As the drug's metabolism involves cytochrome P450 3A, suvorexant should not be used with inhibitors of this enzyme system such as ciprofloxacin, clarithromycin, the azole antifungal drugs and grapefruit juice. Enzyme inducers such as phenytoin reduce the concentration of suvorexant.

In one trial of suvorexant, patients with primary insomnia were randomised to take 10 mg, 20 mg, 40 mg or 80 mg for four weeks.¹ Each group also took a placebo for four weeks. The effect of treatment was assessed by polysomnography. Sleep efficiency was

defined as the ratio of the time asleep to the time spent in bed. At the start of the study, the average sleep efficiency was 66% with a total sleep time of 316 minutes. These measures improved from the first night of active treatment. After four weeks of taking suvorexant, sleep efficiency had improved by 4.7–10.4% and total sleep time had increased by 22–50 minutes.¹

Two placebo-controlled trials randomised a total of 2030 patients with primary insomnia.² In the suvorexant groups 742 patients aged 18–64 years took 20 mg or 40 mg while 521 older people took 15 mg or 30 mg. The patients kept sleep diaries and had polysomnography at intervals during the three months of treatment. From the first night of treatment there was a difference in efficacy between suvorexant and placebo. After one month patients taking suvorexant (15 mg or 20 mg) were falling asleep 5–7 minutes faster and sleeping for 16–21 minutes longer compared with placebo. Similar results were seen at three months (see Table). Rebound insomnia occurred when the patients stopped suvorexant, but this was only statistically significant in one trial for patients stopping the 30 mg or 40 mg dose.²

A one-year trial randomised 781 patients with primary insomnia to take suvorexant or a placebo.³ Patients over 65 years took 30 mg and other patients took 40 mg. After a year, the 322 patients still taking suvorexant either continued it or were switched to placebo. All the patients kept a diary about their sleep. At the start of the study, the patients in the placebo group said it was taking them 65 minutes to get to sleep and they slept for an average of 330 minutes. The corresponding figures for the suvorexant group were 66 minutes and 320 minutes.

Table **Three-month efficacy of suvorexant**

	Suvorexant (15 mg or 20 mg) 493 patients	Placebo 767 patients
Time to sleep onset		
Mean time to sleep onset at baseline	63–86 min	67–81 min
Reduction after three months	23–28 min	17–21 min
Difference from placebo at three months	6–7 min	–
Total sleep time		
Mean total sleep time at baseline	298–322 min	310–316 min
Increase after three months	51–60 min	38–41 min
Difference from placebo at three months	13–19 min	–

Source: Reference 2

When efficacy was assessed over a month the suvorexant group was getting to sleep 18 minutes sooner on average and sleeping for 39 minutes longer than before. These benefits were maintained for the patients who continued treatment for one year. There were no statistically significant differences in symptoms when suvorexant was withdrawn, but the time to sleep onset increased and the total sleep time decreased.³

During the one-year trial approximately 38% of the suvorexant and placebo groups did not complete the study. Adverse events caused 11.7% of the patients taking suvorexant and 8.5% of the placebo group to discontinue. Somnolence affected 13.2% of the patients taking suvorexant but only 2.7% of the placebo group. Other adverse effects which were more frequent with suvorexant were fatigue, dry mouth, dyspepsia and peripheral oedema. Although there was no overall effect on mood, four patients taking suvorexant developed suicidal ideation. Uncommon adverse effects, such as sleep walking, sleep paralysis and hallucinations, were also only reported in the suvorexant group.³

For a hypnotic, suvorexant has a long half-life. Although most patients are not affected, some will have residual effects the next day. They should therefore not drive or operate machinery if they are not fully alert. Alcohol and other drugs that depress the central nervous system should be avoided. The safety of suvorexant in pregnancy and lactation is unknown. Patients with neurological or psychiatric disorders were excluded from the trials.^{2,3} Suvorexant is contraindicated in narcolepsy.

It should be noted that some of the clinical trials used doses that were higher than the doses approved for use in Australia (15 mg and 20 mg). The higher doses had more adverse effects, but the efficacy of suvorexant at lower doses seems modest. In a systematic review, the differences for suvorexant 15 or 20 mg compared with placebo, after three months of treatment, were six minutes for the time to fall asleep and 16 minutes for total sleep time. Thirteen patients need to be treated for one to have a 15% subjective improvement in total sleep time. As 26 would need to be treated for a 15% improvement in the time to sleep onset, this effect is not significant. The systematic review says that for every 28 people taking suvorexant 15 or 20 mg, one would experience somnolence as an adverse event.⁴

While suvorexant may be better than placebo, how it compares with other hypnotics is uncertain. Dependence is less likely to be a problem compared to benzodiazepines, but caution is advised when prescribing suvorexant to people with a history of drug abuse. If a hypnotic is required, suvorexant should not be taken for more than three months without the indication being reviewed.

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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 websites of the Food and Drug Administration in the USA and the Therapeutic Goods Administration.