Melatonin prolonged-release tablets (Circadin) for primary insomnia in older people

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Key points

- Melatonin prolonged-release tablets are approved for short-term treatment (up to 3 weeks) of primary insomnia characterised by poor quality of sleep in people aged ≥ 55 years. They are not PBS listed.
- Non-drug therapies are first line for treating primary insomnia.
- Melatonin is an alternative to a benzodiazepine or related hypnotic (zolpidem or zopiclone) if drug therapy is necessary for persistent primary insomnia.
- In clinical trials, people aged ≥ 55 years who received prolonged-release melatonin gained modest improvements in quality of sleep and morning alertness over those seen with placebo. Clinically meaningful improvements in both outcomes occurred in one-third of patients.
- Prolonged-release melatonin in short-term use has not been associated with impaired daytime alertness, dependence, withdrawal effects or rebound insomnia. Long-term safety is yet to be established.
- There is insufficient evidence at present to support treatment beyond 3 weeks or repeated use after an initial course.

PBS listing

Melatonin (Circadin) is not listed on the PBS.

Place in therapy

Melatonin is a hormone secreted by the pineal gland to regulate circadian rhythm and the sleep–wake cycle.[1] A new prolonged-release melatonin tablet (Circadin) is TGA approved as monotherapy for short-term treatment (up to 3 weeks) of primary insomnia* characterised by poor quality of sleep in patients aged ≥ 55 years.[2]

Endogenous melatonin concentrations increase soon after the onset of night, peak in the early morning (2–4 am) then diminish in response to light.[1,2] The prolonged-release formulation attempts to mimic the physiological release of melatonin, with peak concentrations occurring 1.6–2.6 hours after a dose.[1,2]

Non-drug therapy is first line for primary insomnia.[3,4] If drug therapy becomes necessary for persistent symptoms, melatonin can be used as an alternative to a benzodiazepine or related hypnotic drug (zolpidem or zopiclone).

Unlike benzodiazepines and related drugs, prolonged-release melatonin does not appear to cause impaired daytime alertness, dependence, withdrawal effects or rebound insomnia.

Some people gain clinically important improvements in quality of sleep and morning alertness with prolonged-release melatonin. However, many patients did not respond to treatment in clinical trials, and the magnitude of effect over placebo was modest. If insomnia persists or recurs on stopping melatonin, reconsider underlying causes and use non-drug therapies, if not already implemented.[4]

There is insufficient evidence at present to support treatment beyond 3 weeks, repeated use or use with other hypnotic medicines.[5–7] The efficacy of prolonged-release melatonin in treating primary insomnia has not been established in people aged < 55 years or been directly compared with other medicines or non-drug therapies.

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*Diagnosed as a complaint of difficulty in initiating or maintaining sleep, or of poor quality of sleep, for ≥ 1 month, associated with impaired daytime functioning, and not attributable to any medical or psychiatric condition, substance or environmental cause.[1]

Prolonged-release melatonin improves both quality of sleep and morning alertness in about one-third of patients

Studies investigated the efficacy of prolonged-release melatonin in people aged ≥ 55 years with primary insomnia.[6–8] Overall, more people responded to treatment with melatonin — that is, had a clinically meaningful improvement in both quality of sleep and morning alertness — than with placebo (32% vs 19%).[6,7,9]

In clinical studies, patients in general practice who had persistent complaints of poor sleep quality were randomised to receive prolonged-release melatonin (2 mg at night) or placebo for 3 weeks.[6,7]

Efficacy was primarily assessed by participant self-report using the Leeds Sleep Evaluation Questionnaire (LSEQ).[6,7] This tool consists of 100 mm visual analogue scales that measure the effects of drugs on 4 progressive domains of sleep and morning behaviour.[5–7] Primary efficacy outcomes were based on 2 domains: 'quality of sleep' (extent of wakeful periods and restlessness) and 'behaviour following wakening' (effects on morning alertness, balance and coordination).

Improvements on the LSEQ scales of quality of sleep and behaviour following wakening were statistically significantly greater with prolonged-release melatonin compared with placebo (Table 1(http://www.nps.org.au/publications/health-professional/nps-radar/2010/may-2010/melatonin#Table_1:_Efficacy_of_prolonged-release_melatonin_in_clinical_studies:_Leeds_Sleep_Evaluation_Questionnaire_quality_of_sleep_and_behaviour_following_wakening_scales)). Time to sleep onset was also reduced by melatonin in two studies by about 9 minutes compared with placebo. [5–9]

Table 1 – **Efficacy of prolonged-release melatonin in clinical studies: Leeds Sleep Evaluation Questionnaire quality of sleep and behaviour following wakening scales**[6,7,9]*

Study	Mean change from baseline (mm)†		Improvement with melatonin over placebo ‡
	Melatonin	Placebo	
Neurim VII study (n = 170)			
Quality of sleep	–22.5	–16.5	6 mm
Behaviour following wakening	–15.7	–6.8	9 mm
Neurim IX study (n = 334)			
Quality of sleep	–8.6	–4.2	4 mm
Behaviour following wakening	–7.0	–4.1	3 mm

* Primary efficacy outcome in the Neurim VII study

† Decrease from baseline of ≥ 10 mm on a 100 mm scale is a clinically important improvement[5–7]

‡ Differences between treatment groups are statistically significant

However, mean differences in LSEQ scores between treatment groups were modest (< 10 mm, see Table 1(http://www.nps.org.au/publications/health-professional/nps-radar/2010/may-2010/melatonin#Table_1:_Efficacy_of_prolonged-release_melatonin_in_clinical_studies:_Leeds_Sleep_Evaluation_Questionnaire_quality_of_sleep_and_behaviour_following_wakening_scales)). To establish the clinical relevance of melatonin's effect, 'responder' rates were analysed and found to be statistically significantly higher than for placebo (Table 2(http://www.nps.org.au/publications/health-professional/nps-radar/2010/may-2010/melatonin#Table_2:_Proportion_of_people_in_clinical_studies_who_responded_to_treatment_with_prolonged-release_melatonin_and_placebo)).[5-7,9] The overall proportion of people with a clinically important improvement in quality of sleep (48% vs 35%) or behaviour following awakening alone (40% vs 30%) was also statistically significantly higher with melatonin compared with placebo, respectively.[9]

Table 2 – **Proportion of people in clinical studies who responded to treatment with prolonged-release melatonin or placebo**[6,7]*†

	Clinically important improvement‡	
Study	Melatonin	Placebo
Neurim VII study (n = 170)	47%	27%
Neurim IX study (n = 334)	26%	15%

* Primary efficacy outcome in the Neurim IX study.
† 'Responders' had to demonstrate an improvement of ≥ 10 mm on both 'quality of sleep' and 'behaviour following wakening' 100 mm scales of the Leeds Sleep Evaluation Questionnaire.
‡ Differences between treatment groups are statistically significant.

Concerns about the methodological limitations of the studies with prolonged-release melatonin were raised by regulators during marketing approvals in Australia, Europe and Canada. Nevertheless, studies overall were considered to provide evidence of efficacy, and approval was deemed reasonable given the apparent lack of safety concerns in the short-term (see Safety issues(http://www.nps.org.au/publications/health-professional/nps-radar/2010/may-2010/melatonin#Safety_issues)).[5,9] Issues for regulators mainly related to use of a subset of LSEQ domains to assess efficacy[5,9], although an analysis indicates that this is a valid approach.[10] Exclusion of people who responded to placebo during the run-in period was also questioned[6,7], but this does not appear to have biased results in favour of melatonin.[9]

Treat primary insomnia with non-drug therapies first

Behavioural and cognitive therapies are effective for treating primary insomnia, including in people aged ≥ 55 years.[11-13]Combined with education on good sleep practices, these therapies provide long-lasting improvements in sleep not seen with drug treatment.[13] For more information on non-drug therapies for insomnia, including techniques and instructions for patients, see NPS Prescribing Practice Review 49: Management options for improving sleep(http://www.nps.org.au/publications/health-professional/nps-news/2010/prescribing-practice-review-49).

Safety issues

The safety profile of prolonged-release melatonin in short-term use (≤ 3 weeks) appears to be favourable in people aged ≥ 55 years when compared with placebo. Long-term safety data are currently limited.

The overall rate of adverse events in studies was similar between prolonged-release melatonin and placebo (37% vs 31%).[9] Adverse events most frequently reported in both treatment groups were asthenia, headache, respiratory infections and back pain.[2,5,9] Fewer patients stopped melatonin because of adverse events than they did with placebo (1.3% vs 3.6%). [5]

Safety and efficacy have not been assessed in people with severe psychiatric or neurological diseases, or using psychotropic treatment concurrently or in the previous 3 months (2 weeks for hypnotic drugs).[5–7] Avoid in people with hepatic impairment, as there is no clinical experience of use in these patients.[2]

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online or by using the 'Blue Card' distributed three times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website(http://www.tga.gov.au/).

Short-term use does not appear to cause the usual harms of hypnotic drugs

Studies of prolonged-release melatonin found no increased risk of cognitive impairment and psychomotor adverse events such as falls, fractures and motor vehicle accidents, which are associated with benzodiazepines and other hypnotic drugs, especially in older people.[5,9,14]

Dizziness, loss of consciousness and falls were seldom reported with melatonin.[9] However, studies may not have detected serious or infrequent adverse events, so the possibility of these occurring with melatonin cannot be excluded.

There is currently no evidence to suggest that prolonged-release melatonin causes tolerance, dependence, withdrawal effects or rebound insomnia.[5,6] One study found a decline in efficacy 2 weeks after stopping melatonin, but sleep outcomes remained better than before treatment.[6]

Avoid or use cautiously with certain drugs, hypnotics and alcohol

Fluvoxamine increases melatonin concentrations by inhibiting cytochrome P450 (CYP) 1A2 and 2C19 enzyme metabolism: avoid this combination.[2] Consider melatonin carefully in people receiving cimetidine (CYP2D6 inhibitor), 5- or 8-methoxypsoralen or oestrogen therapy (CYP1A1 and 1A2 inhibitor), as these drugs can also increase melatonin concentrations.[2] Interactions with other CYP1A2 inhibitors (e.g. quinolone antibiotics) and CYP1A2 inducers (e.g. carbamazepine, rifampicin, cigarette smoking) are theoretically possible.[2]

Do not use melatonin with benzodiazepines and related hypnotic drugs: this increases the risk of cognitive and psychomotor adverse effects, and there are no efficacy data for this combination.[2,5]

Avoid concomitant use with alcohol as this may affect the prolonged-release properties of melatonin.[2]

Dosing issues

The recommended dosage of prolonged-release melatonin is a 2 mg tablet taken once daily, 1–2 hours before bedtime.[2](http://www.nps.org.au/publications/health-professional/nps-radar/2010/may-2010/melatonin#fnote2)Tablets must be swallowed whole after food, and not be crushed, chewed or divided.[2] Food delays the absorption of melatonin but does not affect peak concentrations or the total amount absorbed.[2]

Information for patients

Inform patients and carers that prolonged-release melatonin:

- must be taken swallowed whole, 1–2 hours before bedtime
- is for short-term use only (up to 3 weeks)
- should not be taken with alcohol or with other medicines for sleep, including non-prescription and herbal preparations
- currently has limited experience of use, and side effects such as drowsiness are possible
- may affect the ability to drive safely — do not drive or undertake any hazardous activities for a few hours after a dose, or if mental alertness or co-ordination feel impaired.[2]

Ensure that patients and carers understand that melatonin is a medicine. Advise them about good sleep practices for 'natural sleep', such as bright light exposure and exercise (not near bedtime), and encourage them to continue using non-drug therapies for insomnia.

The NPS consumer campaign *Sleep right. Sleep tight* provides patient information leaflets on getting a good night's sleep. These can be ordered or downloaded from www.nps.org.au/sleep(http://www.nps.org.au/sleep). People can also take a sleep quiz on this website, enabling them to assess and report their quality of sleep.

Discuss the Circadin consumer medicine information (CMI) leaflet(http://www.nps.org.au/medicines/brain-and-nervous-system/sedatives-and-medicines-for-sleep-problems/melatonin-sedatives-and-medicines-for-sleep-problems/circadin-tablets) with the patient.

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