

NEW DRUG EVALUATION

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MELATONIN FOR SLEEP DISORDERS IN ADULTS

Melatonin modified-release tablets are now licensed as monotherapy for the short-term treatment of primary insomnia in adults aged ≥ 55 years. The evidence for this therapeutic indication is limited and there are no studies comparing melatonin MR with conventional hypnotics in the licensed population. It appears to be well tolerated in short-term studies and has not been shown to be associated with withdrawal effects. Sleep hygiene and stimulus control advice should be given as first-line treatment prior to initiating any pharmacological therapy.

What is it?

Melatonin is a hormone secreted by the pineal gland. One of its primary functions is regulation of the circadian rhythm and sleep. Based upon its physiological role, exogenous melatonin has been used to manipulate circadian rhythm and induce sleep.¹ Until recently melatonin was only available on a named-patient basis. Melatonin 2 mg modified-release (MR) tablets (Circadin[®], Lundbeck) are now available as monotherapy for the short-term (less than three weeks) treatment of primary insomnia in patients aged ≥ 55 years.^{2,3} Melatonin MR releases melatonin over 8 to 10 hours, mimicking the physiological profile of endogenous melatonin.² The role of melatonin in the management of sleep disorders in children has been reviewed in a previous Drug Update.⁴

How effective is it?

Two, small, randomised, double-blind, placebo-controlled studies have been published.^{5,6} These evaluated the use of melatonin MR 2 mg over 3 weeks (one tablet daily, one to two hours before bedtime) in adults aged ≥ 55 years with a diagnosis of primary insomnia.^{5,6} Patients were excluded if they had used hypnotics within the previous two weeks or had significant psychiatric or neurological disorders. Sleep and morning behaviour were measured using the Leeds Sleep Evaluation Questionnaire (LSEQ),⁷ Pittsburgh Sleep Quality Index,⁸ and other quality of life (WHO-5) and sleep diaries to evaluate sleep and daytime parameters. The primary endpoint evaluated in the first study ($n = 170$), although not clearly stated, was quality of sleep,⁵ which was improved by melatonin MR compared with placebo (-22.5 mm versus -16.5 mm, $p = 0.047$),⁵ and morning alertness, defined as behaviour following wakefulness (-15.7 mm versus -6.8 mm, $p = 0.002$). Secondary outcomes that improved with melatonin MR included sleep quality with an improvement of 0.43 units over placebo ($p = 0.003$). To establish clinical relevance of the observed effect, a responder rate analysis was performed.⁵ A higher proportion of melatonin MR patients were defined as responders, i.e. they had concomitant improvements in quality of sleep and morning alertness of ≥ 10 mm (47% vs. 27%, $p \leq 0.01$). Differences among several other secondary outcome measures failed to reach significance.⁵

A second study ($n = 334$) had a similar primary endpoint to the previous study and used the LSEQ to demonstrate a responder rate of 26% for melatonin MR compared with 15% for placebo ($p = 0.014$; odds ratio = 1.97, 95% confidence interval 1.14 to 3.41).⁶ Melatonin MR also produced benefits in some secondary outcomes including quality of sleep (-4.0 mm, $p = 0.014$), morning alertness (-3.0 mm, $p = 0.038$), getting to sleep (-3.3 mm, $p = 0.013$), and in the WHO-5 well-being index ($p = 0.034$) but not in awakening from sleep (-2.0 mm, $p = 0.16$).⁶ Longer term safety and efficacy of up to 61 weeks have been evaluated in an open-label study.²

Comparative data are limited to small, short-term studies assessing the effects of melatonin MR in healthy volunteers who did not have primary insomnia.^{9,11} One placebo-controlled trial investigated the effect of melatonin on circadian rhythm sleep disorders induced by jet-lag ($n = 30$).⁹ This study demonstrated that both melatonin MR 2 mg and zopiclone 5 mg were significantly more effective than placebo at inducing sleep (7.3 min and 6.7 min vs. 12.3 min respectively, $p < 0.003$ and $p < 0.01$).

How safe is it?

Safety and withdrawal effects of melatonin MR in adults were addressed by pooling data from short- and long-term studies ($n = 1,281$).^{2,5,6} The most common adverse events were headache (5.3%), pharyngitis (4.8%), back pain (3.4%) and asthenia (3.3%), occurring at similar frequency with melatonin MR and placebo during the three week study period.² There was no evidence of withdrawal effects following treatment discontinuation, assessed by the Benzodiazepine Withdrawal Symptom Questionnaire.^{5,12}

In two small studies ($n = 16$ and $n = 23$) psychomotor function and performance (memory recall and driving skills) were not impaired in healthy subjects up to fifteen hours after ingestion of melatonin MR, unlike benzodiazepine and non-benzodiazepine hypnotic comparators.^{10,11}

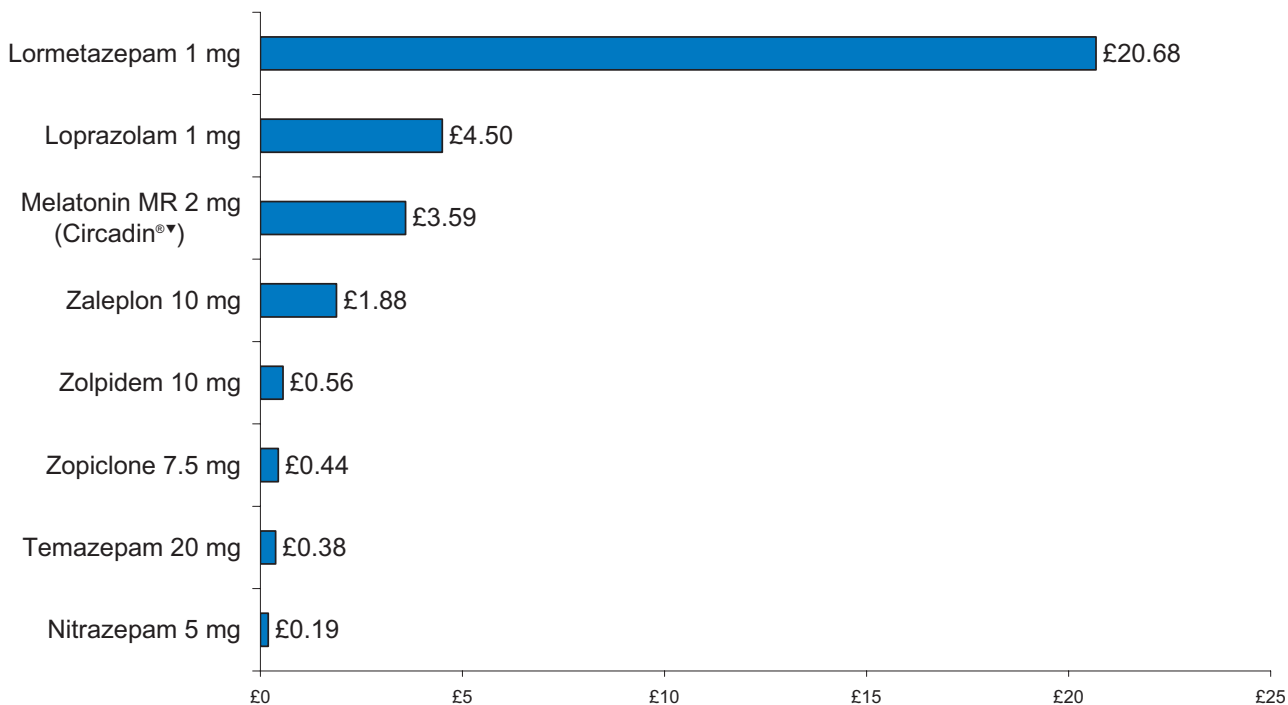
Melatonin is metabolised via cytochromes P450 and altered melatonin concentrations have been demonstrated with a range of enzyme inducers and inhibitors. It is not recommended in patients with hepatic impairment.³

What other options are there?

Primary insomnia (sleeplessness that is not attributable to an underlying psychological or physical condition or drug) occurs in 30% of cases of chronic insomnia.¹³ The first step in its management should incorporate advice on sleep hygiene (e.g. a dark bedroom, relaxing before retiring to bed, avoiding caffeine) and stimulus control (e.g. avoiding sleeping during the day). If this is unsuccessful, a short-course of up to two weeks with a pharmacological treatment may be indicated.¹³ NICE guidance states there is a lack of compelling evidence to distinguish between the available shorter acting hypnotics and the drug with the lowest acquisition cost should be prescribed.¹⁴

How much does it cost?

Cost for 7 days treatment (Drug Tariff and NHS dm+d, July 2008)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

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KEY CT – controlled trial, G – guidance, R – review, RCT – randomised controlled trial, Abs – Abstract, U – unpublished

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