MTRAC
Midlands Therapeutics Review and Advisory Committee

Commissioning Support Melatonin *(Circadin®)*

For the treatment of primary insomnia

Commissioning guidance:

Commissioners may wish to bear the following in mind when considering the commissioning of melatonin:

- MHRA advice that "it is important to ensure that the licensed product available in the UK is used wherever possible. This includes off-label use of the licensed product, if deemed suitable by the clinician."
- The proven efficacy of prolonged release (PR)-melatonin is in patients over the age of 55 with a diagnosis of primary insomnia, and for up to 13 weeks.
- The main effect of melatonin on sleep was to shorten the length of time to fall asleep (sleep latency).

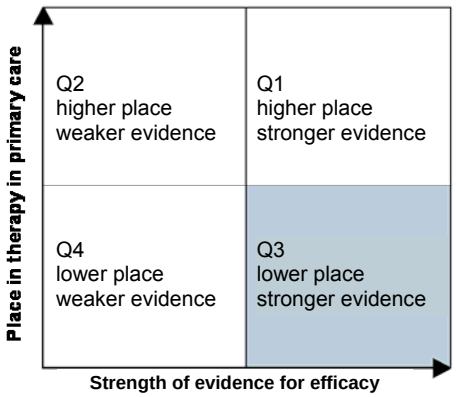
Prescribing guidance: Category A (Q3) **BNF: 4.1.1**

Melatonin is suitable for prescribing in primary care.

Category A: suitable for prescribing in primary care

Q3 rating: The evidence for efficacy of PR-melatonin was based on three randomised, placebo-controlled trials with highly subjective outcomes. Two of the trials showed that PR-melatonin shortened sleep latency times by 9 and 15 minutes respectively more than placebo. None of the trials showed a significant effect on total sleep time. There were no comparisons with other treatments for insomnia, giving PR-melatonin a low place in therapy.

The Q rating relates to the drug's position on the effectiveness indicator grid. *The strength of the evidence is determined by the quality and quantity of studies that show significant efficacy of the drug compared with placebo or alternative therapy. Its place in therapy in primary care takes into account safety and practical aspects of using the drug in primary care, alternative options, relevant NICE guidance, and the need for secondary care input.*



MTRAC updated its guidance on PR-melatonin following the publication of new evidence.

Description of technology

Melatonin is a hormone secreted by the pineal gland. Based upon its physiological role, exogenous melatonin has been used to manipulate circadian rhythm and induce sleep. A prolonged-release (PR) formulation of melatonin was launched in 2008, licensed as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.[1]

The recommended daily dose is 2 mg once daily, taken 1 to 2 hours before bedtime and after food. Treatment may be continued for up to 13 weeks.[1]

Background

Primary insomnia is defined as sleeplessness for at least one month not caused by an underlying psychological (e.g. mental health disorder) or physical condition, or by drug treatment.[2] It may be caused by problems with the sleep environment (e.g. light, noise), irregular sleep routine (i.e. shift work or jet lag) or negative sleep habits (e.g. daytime napping or too much physical arousal prior to retiring).[2] A review of epidemiological studies of insomnia estimated the prevalence of primary insomnia (defined according to DSM-IV criteria) as 2 to 4% of the general population.[3]

The first-line treatment for sleep disorders is the improvement of sleep hygiene.[2] Pharmacological therapies include over-the-counter remedies (diphenhydramine, promethazine), short-acting benzodiazepines (temazepam, loprazolam and lormetazepam), or hypnotic drugs (zopiclone, zolpidem, zaleplon). NICE guidance on the hypnotic drugs[4] (zaleplon, zopiclone and zolpidem) was issued in April 2004 and advised that:

- Pharmacotherapy was only recommended in patients with severe insomnia that interferes with daily life and only for short periods of time in accordance with licensed indications.
- Because of a lack of compelling evidence to distinguish between the newer hypnotic drugs and short-acting benzodiazepines (temazepam, loprazolam, lormetazepam), the drug with the lowest purchase cost should be prescribed.
- Patients who have not responded to one of these hypnotic drugs should not be prescribed any of the others.

Clinical evidence for efficacy and safety

Three double-blind, randomised placebo-controlled trials evaluated the efficacy of PR-melatonin in patients over 55 years of age with a diagnosis of primary insomnia according to DSM-IV criteria.[5-7] In all the trials, patients were excluded if they had used hypnotics within the previous two weeks or had significant psychiatric or neurological disorders.

The NEURIM IX[5] and NEURIM VII[6] trials were of similar design. After a two-week placebo-treatment period, patients who still had poor sleep quality were

randomised to treatment with PR-melatonin 2 mg per day or placebo for three weeks. The main outcome measures were the subscales of the Leeds Sleep Evaluation Questionnaire (LSEQ): quality of sleep (QOS), morning alertness (BFW), getting to sleep (GTS) and awakening from sleep (AFS). A "response to treatment" was defined as a clinically relevant change (> 10 mm on a 100 mm visual analog scale) in both the QOS and BFW subscales. In both trials, patients kept sleep diaries, and a quality of life questionnaire was completed in the larger NEURIM IX trial.[5] Sleep latency and total sleep time were measured as secondary outcomes.

In the NEURIM IX trial (n = 354) the primary outcome was "response to treatment".[5] After three weeks' treatment, 25% (44/177) PR-melatonin-treated patients and 14% (25/177) placebo-treated patients had a "response to treatment" (p = 0.011; Odds Ratio [OR] for melatonin *vs.* placebo = 2.01, 95% CI 1.17 to 3.46, NNT = 9).[5] Mean sleep latency was significantly reduced with PR-melatonin treatment by 9 minutes (95% CI 1.0 to 16.7 minutes) compared with placebo, p = 0.028. There was no significant difference between treatment groups for total sleep time. PR-melatonin-treated patients showed a significantly better score on the WHO-5 well-being index than placebo-treated patients (p = 0.034).

In the NEURIM VII trial (n = 170),[6] the primary outcomes were changes in LSEQ-QOS and BFW subscales. Significantly greater improvements were noted for both scales compared with placebo (placebo-subtracted values of 6 mm on the QOS subscale and 9 mm on the BFW subscale; p ≤ 0.05). There were no significant differences between the treatment groups for the GTS and AFS subscales. A "response to treatment" was recorded in 47% for PR-melatonin *vs.* 27% for placebo (p < 0.01).

A third RCT[7] included data on the efficacy of PR-melatonin in a subgroup of patients aged 65 to 80 (total n = 293). Patients were randomized to treatment with PR-melatonin 2 mg daily or placebo for a three-week treatment period, followed by a 26-week double-blind extension period. The primary outcome of the trial was subjective sleep latency (reported from sleep diaries) after three weeks' treatment. Secondary outcomes were sleep latency, total sleep time and other sleep-related parameters after 26 weeks' treatment.

After three weeks' treatment, sleep latency was significantly shorter in the subgroup of PR-melatonin-treated patients aged 65 to 80 compared with placebo (difference of -15.6 minutes; 95% CI -25.3 to -6.0; p = 0.002). Secondary outcomes such as sleep maintenance, sleep quality, and time of sleep onset were also significantly improved with PR-melatonin compared with placebo. There was no significant difference between PR-melatonin and placebo treatment for the total sleep time.

After 26 weeks' treatment, PR-melatonin-treated patients showed sustained shorter sleep latency times compared with placebo (difference of -14.5 minutes. 95% CI -21.4 to -7.7; p < 0.001). There was no significant difference between treatment groups for total sleep time.

Adverse events

In data submitted for licensing,[8] about 37% of PR-melatonin-treated patients and 31% of placebo-treated patients experienced an adverse event. The most common adverse events were headache, pharyngitis, back pain and asthenia. Dizziness, loss of consciousness and falls were occasionally reported. On stopping treatment, 29% of patients in one trial[6] reported new symptoms: PR-melatonin-treated patients reported widespread tingling and prickling and an unusual taste in the mouth; placebo-treated patients reported feelings of unreality, depression, memory lapses and nausea, and all patients reported muscle pain or spasms.

Considerations for cost impact

- MHRA advice on melatonin[9] is that "it is important to ensure that the licensed product available in the UK is used wherever possible. This includes off-label use of the licensed product, if deemed suitable by the clinician." Importation of unlicensed melatonin products remains possible provided the prescriber gives written details of the special clinical need for each order placed.
- At current prices, the 30-day cost per patient of prescribing the licensed formulation of PR-melatonin 2 mg daily (Circadin) is £15.39.

[Price taken from Drug Tariff, November 2013]

References

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