

Coventry & Warwickshire Area Prescribing Committee



Drug Positioning Statement

DPS002

Melatonin (Circadin® and unlicensed products) – Short term insomnia

Dec 2013

VERDICT

The Coventry & Warwickshire APC recommends that for the indication of short-term insomnia melatonin in all its forms should be initiated by the specialist and then can be prescribed in primary care in accordance with the published shared care agreement. This positioning statement addresses the use of licensed and unlicensed melatonin by specialist clinicians.

Specialist Drugs Status: Shared Care (SC)

Summary notes¹

LICENSED INDICATION: Monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over (the indication of primary insomnia excludes sleeplessness attributable to medical, psychiatric & environmental causes).

PHARMACOLOGICAL ACTION: Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin. Physiologically, melatonin secretion increases soon after the onset of darkness, peaks at 2-4 am and diminishes during the second half of the night. Melatonin is associated with the control of circadian rhythms and entrainment to the light-dark cycle. It is also associated with a hypnotic effect and increased propensity for sleep.

The activity of melatonin at the MT1, MT2 and MT3 receptors is believed to contribute to its sleep-promoting properties, as these receptors (mainly MT1 and MT2) are involved in the regulation of circadian rhythms and sleep regulation.

Because of the role of melatonin in sleep and circadian rhythm regulation, and the age related decrease in endogenous melatonin production, melatonin may effectively improve sleep quality particularly in patients who are over 55 with primary insomnia.

The EMEA review notes that the role of melatonin in regulating sleep and how this role is mediated remains unclear. In vitro, melatonin is described as acting at the central nervous system level possibly involving interaction with melatonin MT1 and MT2 receptor subtypes. There are studies in vivo, but results are difficult to interpret and extrapolate to humans.

PRESENTATION: Circadin® 2mg tablets

DOSE: The recommended dose is 2mg 1-2 hours before bedtime taken after food, for up to 13 weeks.

COST COMPARISON: 21 days supply (BNF 66)

Circadin® 2mg tablets	£10.77
Temazepam 10mg	£ 7.07
Zopiclone 7.5mg	£ 1.06

Drug profile

The European Medicines Agency recommended the granting of marketing authorisation for Circadin® based on a pivotal trial Neurim IX².

Neurim IX was a double-blind, parallel group, randomised, placebo controlled study of efficacy and safety of Circadin® 2mg in the improvement of sleep quality in insomnia patients aged 55-80 years. 334 patients were included in the full analysis set (169 Circadin® and 165 Placebo)

The primary efficacy endpoint for this study was to compare, at the end of a 3-week treatment period, the rate of responders in Circadin® vs placebo groups. The responders were defined as an improvement of 10mm or more on both the Leeds Quality of Sleep (QOS) and Behaviour following Wakefulness (BFW) parameters. Both these scales are subjective – the scales range from 1mm to 100mm, with the patients marking how they rate their quality of sleep, and feelings of awakesness the next day on this scale. An improvement of more than 10mm meant that the patient had experienced a significant difference.

The results of the trial showed that in both the quality of sleep and feelings of alertness the next day, in patients who took Circadin® showed a higher response rate (26% vs 15%, p=0.014).

i.e. treating 20 people with melatonin, you would expect only two extra people to respond, than if you had just given all 20 patients a placebo tablet (5 responders with melatonin, instead of 3 responders with placebo – three quarters of patients given melatonin would show no response at all). The EMEA noted that with both Neurim IX and another similar trial Neurim VII (which also evaluated the efficacy and safety of Circadin® on the QOS and behaviour during the day, in 170 adult insomniac outpatients aged ≥55years. 78 on Circadin® and 86 placebo) “overall the results ... suggest that the product is efficacious with a small effect size and in a relative small fraction of patients”.

Adverse effects:

The overall rate of adverse effects was about 37% in Circadin® and 31% in placebo groups. The most common adverse effects were headache, pharyngitis, back pain and asthenia with a similar frequency between Circadin® and placebo groups.

Current place in therapy

Background

Unlicensed melatonin preparations are already prescribed off-licence to some patients in Coventry and Warwickshire Partnership Trust (e.g. children, learning disabilities). With the launch of Circadin®, the Medicines and Healthcare products Regulatory Agency (MHRA) produced guidance that when melatonin is indicated, the licensed product be used wherever possible – including off-label use of the licensed product, if deemed suitable by the clinician. The reasoning for this being that Circadin® is manufactured to the standards of Good Manufacturing Practice GMP (unlike imported melatonin products which are not required to be manufactured to these standards).

NICE³

The NICE (National Institute for Health and Clinical Excellence) technology appraisal TA77 on insomnia (April 2004) advises that:

NICE has made the following recommendations about the use of zaleplon, zolpidem & zopiclone to treat insomnia.

- NICE recommends that doctors should consider using non-medicine treatments, and then, if they think that a hypnotic medicine is the appropriate way to treat severe insomnia that is interfering with normal daily life, they should prescribe one for only short periods of time and strictly according to the licence for the drug.
- Because there is no firm evidence of differences in the effects of zaleplon, zolpidem, zopiclone and the shorter-acting benzodiazepines, NICE recommends that doctors should prescribe the cheapest drug, taking into account the daily dose required and the cost for each dose.
- Treatment should only be changed from one of these hypnotics to another if side effects occur that are directly related to the medicine.
- If treatment with one of these hypnotic medicines does not work, the doctor should not prescribe one of the others.

MTRAC⁴

MTRAC (the Midlands Therapeutics Review & Advisory Committee) reviewed the position of Circadin® in October 2013 and issued advice that melatonin 2mg controlled release (Circadin®) is suitable for prescribing in primary care.

Policy Statement^{5,6,7}

For Adult/Older Age Mental Health

Coventry and Warwickshire Partnership Trust recommend that Circadin® is only prescribed within its licensed indication after recommendations in NICE TA77 have been trialed and found ineffective i.e. prescribed in place of other hypnotics to which side-effects have occurred, or where these are not appropriate. Circadin® is currently significantly more expensive than the other licensed hypnotics.

Where a patient has failed to respond to the treatment suggested within the NICE Guidelines and is felt to have individual clinical circumstances that could make them an exception to the policy set out above, Circadin® treatment may only be initiated directly by a Consultant Psychiatrist (or Staff Grade/Specialist Registrar acting under the Consultant's direction). This would be an unlicensed use of Circadin®.

This use should be notified to the Partnership Trust Chief Pharmacist (to allow monitoring/review of this Policy and use of the drug).

Children/Adolescent/People with Learning Disabilities:

Following the MHRA advice, the modified release Circadin® formulation is the preferred choice for children and adolescents – or learning disability and other service users. If there are swallowing difficulties, the tablet can be crushed to a fine powder and mixed with water or given with a small amount of cold soft food such as a teaspoon of yoghurt or jam. If crushing is not an option, there are sources of melatonin manufactured in the UK according to GMP guidance and these are the preferred option to Circadin®. CWPT preferred alternative choices in this situation are Melatonin capsules (Special Products Ltd) 2mg or 3mg, or Melatonin liquid 1mg in 1ml (Special Products Ltd).

References

- 1: <http://emc.medicines.org.uk>
- 2: <http://www.emea.europa.eu/> - EMEA Assessment report for Circadin Procedure No. EMEA/H/C/695
- 3: <http://www.nice.org.uk/TA077>
- 4: MTRAC review at - <http://centreformedicineoptimisation.co.uk/download/e05ecb5a0f02501f91d68e5c368d7e38/Melatonin-Verdict-Update-Oct-2013.pdf>
- 5: East Lancashire Medicines Management Board New Drug Recommendation Circadin 7/2008, UKPPG email group
- 6: CWPT Preferred Prescribing List 2011
- 7: CWPT Recommended Melatonin Products CAMHS/LD sleep disorders 2011