HERTFORDSHIRE MEDICINES MANAGEMENT COMMITTEE

New Drugs for Insomnia– Circadin and Ramelteon

Drug	Indication	Date last revised	Status	NICE / SMC Guidance
Circadin® (Melatonin m/r) **Rozerem ®** (Ramelteon)	Licensed Indication: **Circadin:** monotherapy for short-term (≤ three weeks) treatment of primary insomnia in patients aged 55 or over. **Ramelteon: Not yet licensed** An application for a Marketing Authorisation for the management of primary insomnia in adults has been submitted to the EMEA. Expected that any licence will allow for a maximum of six months of treatment.	19th Sept 08	Final	NICE: Not assessed SMC: Not assessed

HMMC Recommendation

NOT recommended for the management of Primary Insomnia based on the evidence presented.

- There are currently limited efficacy and safety data on these drugs.
- The two trials for Circadin have demonstrated that some older people treated with m/r melatonin for 3 weeks will have an improvement in quality of sleep and morning awakeness, but only a minority will benefit over 3 weeks.
- A small improvement in sleep latency (about 9 minutes) was found, as a secondary end-point, which is a similar magnitude to that found in trials of benzodiazepines, Z-drugs and ramelteon (not yet licensed).
- Since these are relatively new drugs, there is not enough evidence to suggest that these drugs are associated with less withdrawal and side effects than other hypnotics.

Specific issues for local consideration

- Approximately 20, 000 patients in each PCT (patients > 55years) would seek medical advice for Insomnia related symptoms from a healthcare professional.
- Cost of these drugs are significantly greater than current therapy and cost-effectiveness has yet to be established.
- Safety data:
  More data are required to establish the long-term adverse event profile of both drugs. In a six-month study, 32% of ramelteon recipients experienced raised prolactin levels compared with 19% on placebo.
- Both drugs have restricted evidence. Circadin is only licensed for primary insomnia in adults over 55yrs. Ramelteon will most probably only be licensed for primary insomnia. Current trials for ramelteon (not including open label, unpublished data) have been conducted in elderly patients – similar restriction.

Evidence considered by the Group

Circadin: There are 2 randomised, double-blind, placebo-controlled trials which evaluated the use of melatonin-PR 2 mg once daily, in adults aged 55 or older with a diagnosis of primary insomnia.

- *Study 1:* (n = 170). Primary endpoint: The efficacy of melatonin-PR on quality of sleep (QOS) and behaviour following wakefulness (BFW). Melatonin-PR statistically significantly improved QOS compared with placebo (-22.5 mm vs. -16.5 mm, p = 0.047) and BFW (-15.7 mm vs. -6.8 mm, p = 0.002). Secondary outcomes, **ease of getting to sleep and awakening from sleep, were not significantly different in the two groups**.
- *Study 2:* (n=334). The primary end-point was improvements of 10mm or more on both QOS and BFW. Both scales are 100mm in total. Sleep latency (time to falling asleep) was included as a secondary end-point. Intention-to-treat analysis showed 25% of patients in the m/r melatonin group met the primary end-point vs. 14% in the placebo group. **Sleep latency was 8.8 minutes shorter for melatonin patients compared to placebo** (95% CI 1.0 to 16.7, P=0.028).

Both studies were sponsored by Neurim pharmaceuticals.

Ramelteon: There are seven phase III, randomised, double-blind, placebo-controlled clinical trials Open label, unpublished studies will not be considered.

- *Study 1:* (n=829). Placebo controlled double blind trial. Elderly patients. Randomised to either Ramelteon 4mg, 8mg or placebo. Primary outcome: Mean latency to persistent sleep (mins) was 70mins for Ramelteon 4mg and 8mg and 78.5mins for placebo (p=0.008).
- *Study 2:* (n=100: Elderly). Placebo controlled 3-way, randomised, crossover study: Received either ramelteon 4mg, 8mg or placebo for 2 nights. Primary efficacy measure was mean LPS (Latency to persistent sleep) for each 2-night treatment period. Compared with placebo (38.4 minutes), statistically significant reductions in LPS were seen for ramelteon 4mg (28.7 minutes; P<0.001) and 8mg (30.8 minutes; P=0.005).

There are no head-to-head studies comparing any of these products with current therapy such as the Z drugs. Since these are relatively new drugs, there is not enough evidence to suggest that these drugs are associated with less withdrawal and side effects than other hypnotics. It is therefore difficult to ascertain where in the treatment pathway these would fit in.

See detailed summary for additional information.