HERTFORDSHIRE MEDICINES MANAGEMENT COMMITTEE (HMMC)

MELATONIN FOR INSOMNIA IN CHILDREN

NOT RECOMMENDED

<table>
<thead>
<tr>
<th>Name: generic (trade)</th>
<th>What it is</th>
<th>Indication</th>
<th>Date decision last revised</th>
<th>Decision status</th>
<th>NICE / SMC Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin (Circadin® as an “off label” use, and other unlicensed preparations)</td>
<td>Naturally occurring hormone, assisting in coordination of sleep-wake cycle</td>
<td>Treatment of paediatric sleep disorders</td>
<td>September 2013 (original evidence assessment Feb 2012 and specialist comment reviewed by HMMC April 2012)</td>
<td>Interim</td>
<td>NICE – No Technology appraisal. Evidence Summary, Unlicensed or Off label Medicine 2, published 04/01/2013 SMC – Not recommended for adults, no recommendation in children</td>
</tr>
</tbody>
</table>

HMMC Recommendation:

FOR NEW PATIENTS:
- NOT RECOMMENDED FOR PRESCRIBING BY GPs.
- Specialists initiating any new patients on melatonin must retain prescribing responsibility.

EXISTING PATIENTS:
- For existing patients receiving prescriptions from GPs, it is advised to continue treatment only where benefit has been demonstrated.

Recommendation will be reviewed upon submission of a clear proposal by specialists outlining the key groups of children to be treated, the threshold of dysfunction at which the treatment would be considered, the time period over which melatonin would be prescribed before initial assessment, and clarity around the level of improvement deemed to be a significant improvement such that ongoing treatment is warranted.

Rationale for recommendation

**EFFICACY**
- There are no high quality studies for the off-label use of prolonged release melatonin in children with sleep disorders and ADHD
- Limited short term evidence of benefit exists for unlicensed melatonin in reducing time to sleep onset in children with ADHD by approx 20 minutes and approximately 15-20 minute improvement in average sleep duration. Improvement in ADHD-related behaviour, cognition or quality of life was not robustly demonstrated.
- Longer term efficacy is uncertain.
- Less evidence in other groups of patients, with most robust and recent evidence suggesting lack of meaningful effect.

**SAFETY**
- Usually well tolerated. Mild, transient adverse effects reported in trials: headache, hyperactivity, dizziness and abdominal pain.
- Limited long term safety data.

**COST**
- Unlicensed products vary widely in price.
- Circadin® 2mg M/R tablets cost £15.39 for 30
- Specials listed in October 2013 Drug Tariff:
  - melatonin 5mg/5ml oral suspension x100ml £143.47
  - melatonin 5mg/5ml oral solution x200ml £106.03

**PATIENT FACTORS**
- The effect of a child’s sleep disorder on his/her behaviour, education and on the wider family may be marked, but there is minimal evidence to substantiate melatonin improves these outcomes.

This HMMC recommendation is based upon the evidence available at the time of publication. The recommendation will be reviewed upon request in the light of new evidence becoming available.
Assessment against Ethical Framework

1) Clinical Effectiveness
- Melatonin is prescribed for sleep disorders in patients with a number of underlying conditions, the most common of which are autism, ADHD, learning difficulties, visual impairment and other specific sleep disorders.
- For ADHD, limited evidence is available from 2 small, short-term randomised controlled trials (n=105, t=4 weeks and n=19, t=10 days) and one small long-term follow up study (n=94, mean treatment time 18 months, mean follow up time 3.7 years) with immediate release melatonin (unlicensed).
  - It was demonstrated that 3-6mg melatonin taken immediately before bedtime may improve sleep onset by approximately 20 minutes and sleep duration by 15 to 20 minutes. In the larger short term trial, patients were not taking stimulant treatments for their ADHD.
  - The most common adverse effects reported in the short term trials were headache, hyperactivity, dizziness and abdominal pain. 1 patient reported migraine, assessed as a severe side effect. No adverse effects required further treatment and none necessitated withdrawal from study.
  - The most common adverse effects reported in the long term follow up study were dizziness, sleep maintenance insomnia and bedwetting. 3 children discontinued treatment due to adverse effects: profuse perspiration, persistent dizziness with visual disturbances, headache and daytime laziness; and headache with abdominal pain, nausea and excessive morning sedation.
- A systematic review in children with neurodevelopmental disability and sleep impairment included 3 randomised controlled, crossover design trials of immediate release melatonin in 35 children. A decrease in time to sleep onset was reported, but no effect on total sleep time, night time awakening, or parental opinion.
- Two meta-analyses, which included both adults and children, have been reported, one examining primary sleep disorders and the other secondary sleep disorders. There was some overlap between trials included and those included in the systematic review. Results are difficult to interpret as both adults and children were treated in the included trials.
- A further 6 studies in neurodevelopmental and Autistic Spectrum Disorder (ASD) groups were considered in the evidence evaluation presented to HMMC, February 2012; the largest and most recent was a 2011 randomised, double blind, placebo controlled UK multicentre study in 146 patients (MENDS). This final study concluded that the difference in mean total sleep time between melatonin and placebo groups was almost 16 minutes, and concluded that melatonin does not improve sleep time by a significant amount.

2) Cost of Treatment and Cost effectiveness
- There is no information on cost effectiveness.
- Cost of treatment

<table>
<thead>
<tr>
<th>Drug &amp; Dosage</th>
<th>30 day cost/per patient (assuming 2mg/day dose and 30 day shelf life)</th>
<th>Annual cost per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin modified release (Circadin®) 2mg/day</td>
<td>£15.39</td>
<td>£188</td>
</tr>
<tr>
<td>Melatonin oral suspension 5mg/5ml (unlicensed)</td>
<td>£143.47</td>
<td>£1721.64</td>
</tr>
<tr>
<td>Melatonin 5mg/5ml oral solution (unlicensed)</td>
<td>£106.03</td>
<td>£1272.36</td>
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- Prescribing of Circadin® is an off label use in children.
- Prescription cost analysis in England from July 2011 to July 2012 in general practice for all indications showed that Circadin® accounted for 44% of total melatonin prescribing and 16% of cost, with unlicensed melatonin accounting for 56% of prescribing and 84% of cost.
- The costs of other, solid oral preparations of melatonin are unregulated and can vary widely.
- Hertfordshire annual expenditure was calculated in April 2012 to be approximately £230k.

3) Needs of the population
- The needs of the population may be considered high as there are no alternative medications available and there is both poor access to sleep hygiene behavioural measures. Certain groups of patients are particularly unlikely to respond to such behavioural measures in any case (e.g. ASD patients). The impact of sleep disorders in children must be considered in conjunction with the impact on the wider family.

4) Needs of the community
- The need for healthcare may appear to be low as this group represents a small population within Hertfordshire. However, the high cost of melatonin, in particular the unlicensed preparations, may affect the ability of the local health economy to provide other health interventions.

5) Equity
- None identified

6) Policy drivers
- Local prescribing practice

7) Implementability
- Already widespread prescribing in secondary and primary care. Disinvestment from this treatment may therefore be challenging.

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