**HERTFORDSHIRE MEDICINES MANAGEMENT COMMITTEE (HMMC)**

**MELATONIN FOR INSOMNIA IN CHILDREN**

**RECOMMENDED FOR RESTRICTED USE (AMBER INITIATION)**

<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>February 2020 (original evidence assessment Feb 2012 and specialist comment reviewed by HMMC April 2012 and September 2013)</td>
<td>Final</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>
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</table>

**HMMC Recommendation:**

*Melatonin is recommended for restricted use (Amber Initiation) for the treatment of sleep disturbances in children (under the age of 18 years) with a formal confirmed diagnosis of Autism Spectrum Disorder (ASD) or a formal confirmed diagnosis of attention deficit hyperactivity disorder (ADHD). This approval is subject to use in line with the HMMC approved Prescribing Support Document ‘Melatonin in Neurodevelopmental Disorders in patients under the age of 18 years’, available on the HVCCG and ENHCCG websites.*

**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.
- A trial conducted in 125 children with ASD or Smith-Magenis Syndrome (SMS) found an improvement in total sleep time of 32 minutes and an improvement in sleep latency of 25 minutes. Melatonin did not significantly improve the number of awakenings per night, wake time after sleep onset, composite sleep disturbance index and overall daytime behaviour.

**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 (Drug Tariff, September 2020).
- Ascomel (melatonin) 1mg/ml suspension x 100ml (unlicensed) £44.

**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.

**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 ASD, ADHD, learning difficulties, visual impairment and other specific sleep disorders.

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.
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. One 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. Three 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 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.

The pivotal trial used for the licence application for Slenyto® (prolonged release melatonin tablets) was conducted in 125 children with ASD or SMS and sleep disturbances despite sleep hygiene and behavioural interventions. Children were aged 2-17 years (mean age 8.7 years +/- 4.15 years). The trial consisted of a 13-week randomised placebo-controlled trial (RCT) followed by a 91-week open-label study. Seventy-two children completed the full study. At 52 weeks the following melatonin P/R doses were used in the evening: 2mg (22%); 5mg (36%) 10mg (42%). The average daily dose was 5.3mg. Only four children with SMS were included, the remainder had ASD. 28.8% children also had a concomitant diagnosis of ADHD. Over half the children (65.6%) had taken melatonin prior to study entry, mostly immediate release melatonin (88%) and some controlled release (6%). In the 13-week RCT, Total Sleep Time (TST) improved by 32.43 minutes (p=0.034) and sleep latency (SL-time until falling asleep in evening) improved by 25.30 minutes (p=0.011) with melatonin compared to the placebo group. There was improvement in the duration of uninterrupted sleep, but this did not reach statistical significance at 13 weeks. Although, Slenyto® did induce positive effects on both sleep latency and total sleep time, it did not significantly improve the number of awakenings per night, wake time after sleep onset, composite sleep disturbance index and overall daytime behaviour. Caregivers daytime sleepiness or quality of sleep at night showed no statistically significant differences. Treatment effects on child behaviour and caregivers quality of life were evaluated. Melatonin treatment resulted in significant improvement in externalizing but not internalising behaviour (Strengths and Difficulties questionnaire; SDQ) compared to placebo (p = 0.021) with clinically relevant improvements in 53.7% of melatonin treated versus 27.6% of placebo treated children (p = 0.008). Caregivers quality of life also improved with melatonin versus placebo (p = 0.010) and correlated with the change in total SDQ (p = 0.0005). Melatonin alleviated insomnia-related difficulties, particularly externalising behaviour in the children, subsequently improving caregivers quality of life.
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 8-week expiry for suspension once opened)</th>
<th>Annual cost per patient</th>
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<tbody>
<tr>
<td>Melatonin modified release (Circadin®) 2mg/day</td>
<td>£15.39</td>
<td>£188</td>
</tr>
<tr>
<td>Ascomel (melatonin) 1mg/ml suspension (unlicensed)</td>
<td>£66.00</td>
<td>£803</td>
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- Prescribing of Circadin® is an off label use in children.
- The costs of other, solid oral preparations of melatonin are unregulated and can vary widely.
- Hertfordshire annual expenditure on melatonin products (primary and secondary care) was calculated in October 2019 to be approximately £413k.

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 and newly licensed Slenyto®, may affect the ability of the local health economy to provide other health interventions.

5) **Equity**
   Patients with neurodevelopmental disorders are considered to be disabled under the Equality Act 2010. Agreement by HMMC for GP prescribing of melatonin (for children with neurodevelopmental disorders) is positive as it simplifies access to repeat prescriptions of melatonin for this group of disabled people.

6) **Policy drivers**
   Local prescribing practice.

7) **Implementability**
   Already widespread prescribing in secondary and primary care.

**References**


14. PrescQIPP Bulletin 245, Melatonin. Published July 2019