Appendix 4I - Melatonin Guidance for the treatment of sleep-wake cycle disorders in children

Background

Sleep disturbance in children with neurological or behavioural disorders is common and can be a major source of distress for the patient and the family. Furthermore, sleep disturbances can have an impact on the child’s behaviour and ability to concentrate during the day. In ADHD for example, up to 70% of children experience sleep problems and stimulant medication may contribute to this.

Melatonin is an endogenous hormone produced by the pineal gland in the brain. It is important in the regulation of circadian rhythms.

Melatonin is available as a licensed prolonged release formulation (Circadin® 2mg tablets). It is licensed for short term use in the treatment of insomnia in patients aged over 55. Use of Circadin® in children with sleep disorders is an off-label use.

Alternative formulations of melatonin (Bio-melatonin®, immediate release capsules and liquid formulations) are all unlicensed.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using melatonin outside its authorised indications or using an unlicensed formulation. The MHRA advise that a licensed preparation should be considered first, even if it is for an off label use as the quality is then assured and this is safer than an unlicensed product.

No high-quality evidence is available for the efficacy of Circadin® in children with sleep disorders and ADHD.

There is limited evidence, from 2 small RCTs and a long-term follow-up study on the safety and efficacy of unlicensed melatonin in stimulant and non-stimulant treated children with ADHD experiencing sleep problems. The evidence is applicable to children aged 6 to 14 years with ADHD and sleep onset insomnia, using unlicensed melatonin (3–6 mg daily) shortly before bedtime. The evidence indicates that unlicensed melatonin used in these RCTs may reduce sleep onset latency by approximately 20 minutes and may improve average sleep duration by 15 to 20 minutes when taken for between 10 days and 4 weeks. Associated improvement in ADHD-related behaviour, cognition or quality of life was not robustly demonstrated.

Discontinuation of unlicensed melatonin led to relapse of sleep onset insomnia in most of the cases where it was used for more than 30 days. Longer term efficacy is unclear.

In children with autism spectrum disorder, NICE guidelines recommend not using a pharmacological intervention to improve sleep unless problems persist despite following a sleep plan, and if such problems are having a negative impact on the child and their family.
**Prior to Initiation Of Melatonin**

Consider adjusting the dose of any stimulant medication if child is struggling to settle in the evening. e.g. reducing the total dose, changing the regimen or formulation so that less medication is administered later in the day, adding a third dose of stimulant in the evening if sleep-onset delay is due to a rebound effect or switching to an agent associated with fewer sleep difficulties (e.g. atomoxetine).

A sleep chart or diary should be completed by parent/carer for a minimum 2 week period and during school term time only, highlighting problems with sleep latency despite use of non-pharmacological measures.

A trial of behavioural intervention or sleep hygiene measures for a minimum of 2 months. If trial successful, measures should be continued without prescribing of melatonin. If trial fails, melatonin should be considered for prescribing along with behavioural interventions/sleep hygiene measures.

Simple non-pharmacological measures include:

- Ensuring that there is an established bedtime routine and that a realistic sleep-wake schedule has been agreed.
- Ensuring that the room conditions (temperature, light and noise) are at an optimum level to promote sleep (e.g. minimise background noise, use of a blackout blind)
- Ensuring no late afternoon/evening caffeine consumption.
- Removing television and electronic devices from the child’s room, since it is known that the blue green light emitted by these screens can disturb sleep. Children should avoid looking at bright screens beginning 2-3 hours before bed.

Engagement from the family is vital and there may be instances when it is difficult or impossible to establish behavioural interventions or sleep hygiene measures because the patient and/or family are struggling to cope with the current situation. In these instances, melatonin may be initiated at the same time as behavioural interventions or sleep hygiene measures and consideration of withdrawal once the other interventions are established.

**Indication**

Sleep disorders in children (age 3 to 18 years) with attention deficit hyperactive disorder, autism, visual impairment, learning difficulties and developmental delay where symptoms have been present for at least 6 months or sleep disturbance is so severe that the family are heading for crisis.

Continued use in adulthood when the medication was initiated in childhood for above indication and proved effective.

**Formulary Products**

Melatonin m/r tablets 2mg (Circadin®) is the formulary product on the basis of licensing, cost and quality of the product. It can be given whole or halved which retains the slow release profile or may be crushed to give an immediate release profile.
## Costs (Based on 6mg dose)

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulary</th>
<th>Cost per pack</th>
<th>Cost per year*</th>
<th>Suitable for GP Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin m/r tablets 2mg (Circadin®) (off-label use)</td>
<td>Yes</td>
<td>£15.39 (30)</td>
<td>£562</td>
<td>Yes, up to 10mg dose.</td>
</tr>
<tr>
<td>Melatonin oral solution 1mg/1ml (unlicensed use)</td>
<td>No</td>
<td>£97.00 (200mls)</td>
<td>£1062</td>
<td>No</td>
</tr>
<tr>
<td>Melatonin tablets 3mg (Biomelatonin) (unlicensed use)</td>
<td>No</td>
<td>£60.20 (60)</td>
<td>£732</td>
<td>No</td>
</tr>
</tbody>
</table>

*Scottish Drug Tariff Part 7s December 2015 and BNF September 2015

## Prescribing Information

Melatonin should be initiated at 2mg at night and increased by 2 mg depending on response every 7-14 days up to a maximum of 10mg. Benefits of using doses above 6-9mg are uncertain.

Melatonin m/r tablets 2mg (Circadin®) should be taken 1-2 hours before expected bedtime and after food. Tablets should be swallowed whole but can also be halved using a tablet cutter and still maintain the controlled release profile.

If an immediate release profile is desired or patient has swallowing difficulties, Melatonin m/r tablets 2mg (Circadin®) should be crushed and dispersed in water to provide a “standard release” dose and taken 20-30 minutes before bedtime and after food. Crushed tablets may also be mixed with small amount of soft food e.g. yoghurt or jam (immediately prior to dose) if preferred.

Please see Crushing Melatonin Leaflet (Appendix 1)

In patients taking both crushed and whole or half Melatonin m/r tablets, the dose should be taken 20-30 minutes before bedtime and after food.

If Melatonin becomes ineffective, the timing of administration should be checked.

If Melatonin has successfully established a good sleep pattern, where appropriate a trial withdrawal of melatonin over 2-3 weeks should be undertaken by the specialist 3-6 months following initiation. The continued need for melatonin should be assessed periodically by the specialist, by the medication being reduced or stopped for up to a minimum of 2-3 weeks every 12 months.

Melatonin is generally well tolerated. Full adverse effect profile is unclear due to small size of trials in children. The most commonly reported side effects are: headache, dizziness, nausea and drowsiness.

Co-prescribing of Melatonin and other agents used to promote sleep is not recommended.
No clinically significant drug interactions reported in the literature. Possible interactions of melatonin with other medicinal products have not been fully characterised. Interaction of melatonin with selective serotonin re-uptake inhibitors has been observed.

Caution is also advised in children with autoimmune, renal and hepatic disorders due to limited safety data and in those with lactose intolerance. It can affect seizure control in patients with epilepsy and should be closely monitored. Concerns have also been raised about it causing delays in the onset of puberty, based on animal studies.

Off-label use should be discussed with patient/parent and recorded in the notes.

Feeding tubes- Melatonin m/r tablets 2mg (Circadin®) may be crushed to fine powder and mixed with 15-30mls of water. Tube should be flushed with 30ml water before and after medication given.

In **exceptional circumstances** there may be a need to prescribe unlicensed Melatonin oral solution 1mg/1ml or melatonin MR capsules. These will be prescribed by the specialist along with a letter of special clinical need and responsibility for ongoing prescribing will stay with the specialist.

Please see Melatonin GP Form (Appendix 2)

### Secondary Care / Managed Services Responsibilities

- Initiation of prescription and titration of dose to the optimum level using the minimum effective dose.
- Monitoring of response and adverse drug reactions (ADRs) during the titration period.
- Liaison with general practitioner (GP) when a stable dose has been achieved and proven benefit has been established.
- Provide GP with initiation letter within 14 days of seeing patient including diagnosis, dose of melatonin that patient is stabilised on, treatment plan, duration of treatment before consultant review and state whether specialist or GP will continue prescribing.
- Review patients 2-3 months after initiation, and 6 months thereafter and GP to be notified of any changes within 14 days. A trial withdrawal should be considered at each medication review.
- In the event that the patient does not attend review meetings on two consecutive occasions, the specialist will discharge the patient and advise the GP by letter that in the absence of follow up, continued supply of medication can no longer be recommended.
- Discontinuation in late adolescence (by 18 years) or if necessary, arrange transfer to adult services when child is 18.

### GP Responsibilities

- Monitoring the child’s overall health and well being.
- Informing the secondary care/ managed services clinician of any ADRs observed or any abnormalities from physical checks.
**Prescribe ongoing supplies of melatonin (Circadin®) for doses up to 10mgs.**

**Patient/ Parent Responsibilities**
- Ensure that behavioural interventions/sleep hygiene measures continue to be implemented even whilst on medication.
- Ensure compliance with medication.

**Further Information**
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Margery Reid, Paediatric Pharmacist margery.reid@nhs.net
Crushing Melatonin (Circadin®) MR Tablets

If you have been prescribed Melatonin MR (Circadin®) tablets or if your prescription has changed to Melatonin MR (Circadin®) tablets from an alternative product, you may have been asked to crush the tablets prior to taking the dose. Crushed tablets may be mixed with a little water, or soft food, e.g. yoghurt or jam to aid swallowing.

Crushing tablets is quite simple. You can do it using either a tablet crusher or two spoons. You can purchase a tablet crusher from your local community pharmacy. They cost just a few pounds and are re-usable - just rinse and dry after use.

You can also place the tablet between two dessert spoons to crush it.

- The spoons should be arranged so that one spoon sits in the spoon below.
- Make a small gap between the spoons and place one tablet in the gap between the spoons.
- Gently squeeze the spoons together so that the tablet breaks up, but does not shoot out.
- You only need to roughly crush the tablet - it is not necessary to crush it into a fine powder.
- Repeat if more than one tablet is required to provide the dose.

If you have any questions on crushing your tablets, you can talk to your Community Pharmacist.
TO BE COMPLETED BY THE PRESCRIBER ONLY

A separate form needs to completed by each prescriber

To whom it may concern,

The European licensed products (Circadin® 2mg SR tablet and Bio-Melatonin® 3mg tablet) are unsuitable for my patient(s) because of specific special clinical need(s). Therefore I wish to prescribe the following product(s).

Please list the preparation(s) of melatonin you have occasion to prescribe to your patient(s). | Please state the special clinical need* why your patient(s) are unable to take the licensed tablets (Circadin® or Bio-Melatonin®)
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| | |
| | |
| | |

* examples of special clinical need include the following but are not exhaustive-  
  - Patient is stable on current medication and should not be changed  
  - Patient on a 1mg dose and there is no direct alternative  
  - Patient unable to swallow tablets,  
  - Patient needs a capsule formulation so that the capsule can be broken or sprinkled onto food to help swallowing difficulties  
  - Dosage that patient is on is not suitable for an M/R product and patient needs a standard release product instead  
  - Patient is stable on current medication and should not be changed,

I am aware that the product(s) are unlicensed in the UK and are not a pharmaceutical in the country of origin and may not be manufactured to normally expected standards of pharmaceutical GMP.

Signed__________________________  GMC Number  ____________________

Name____________________________ (Block Capitals Please)

Date__________________________

Once completed forward form to the community / hospital pharmacy for ordering.