SHARED CARE PRESCRIBING GUIDELINE

MELATONIN - Circadin® (off label use)
MELATONIN oral solution 5mg/5ml (Drug Tariff listed unlicensed special)
for the Treatment of Persistent Sleep Disorders in Children over 3 years old with Neurodevelopmental Disorders

Prescribing Clinical Network classification: Amber*

Amber*: Drugs that require initiation by a specialist in secondary / tertiary care but due to more widespread experience in primary care GPs are generally happy to prescribe on specialist advice without the need for a formal shared care protocol. This information sheet is available on the internet http://pad.res360.net/ forming part of the Prescribing Advisory Database (PAD) giving GPs appropriate advice / guidance and is not required to be sent to the GP with the clinic letter. A minimum of one month supply of medication will be provided by the initiating consultant.

N.B. The eligibility criteria included here apply to new patients commencing treatment under this guideline & not to existing patients whose treatment was initiated under the previous version. However, monitoring and discontinuation criteria apply to all patients.
This information sheet does not replace the SPC, which should be read in conjunction with this guidance. Prescribers should also refer to the appropriate paragraph in the current edition of the BNF-C.

Introduction
Insomnia is a widespread problem in children with neurodevelopmental or psychiatric disorders such as autistic spectrum disorder and attention deficit hyperactivity disorder (ADHD).

Behavioural therapy can be very effective in some forms of paediatric insomnia however children with neuropsychiatric disorders tend to have a lower response rate to behavioural therapy and may require drug treatment.

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone produced by the pineal gland during the dark hours of the day and night which appears to support the normal circadian rhythm and aid sleep onset. It is used as a treatment of sleep disorders in children. It is most helpful where sleep onset is a significant problem, but is rarely useful to maintain sleep if a child is waking during the night. Melatonin should not be used in isolation but should be combined with a behavioural programme, involving Clinical Psychology where necessary. The use of a weekly sleep diary before and during treatment will assist the monitoring of response.

The use of Melatonin is supported by NICE in their Clinical Guidelines on the diagnosis and management of chronic fatigue syndrome / myalgic encephalomyelitis (CFS/ME) in adults and children (CG53, 2007). The guideline states that Melatonin may be considered for children and adolescents with CFS/ME who have sleep difficulties, but only under specialist supervision.

Short term use of Melatonin may also occasionally be useful in a range of isolated circumstances where other methods have failed. It should not be considered in the management of sleep problems in otherwise normal children.

Once a regular sleep pattern has successfully been achieved and maintained, there should be a trial withdrawal of treatment. In some children with neurodevelopmental / psychiatric problems, longer term treatment may be needed, but intermittent trials off treatment should be considered.

Currently there are no licensed treatments for sleep disorders in children in the UK. Circadin® is the only UK licensed product which contains Melatonin. It is a 2mg prolonged release tablet. It is licensed for the short-term treatment of primary insomnia characterised by poor quality sleep patterns in patients who are aged 55 or over. The Medicines and Healthcare products Regulatory Agency (MHRA) would prefer an ‘off-label’ licensed product to be used if it can meet the clinical need, rather than an unassessed, unlicensed product. Circadin® should therefore be used wherever possible.

Circadin consists of an immediate release part and then sustained release. If the child is finding it hard to fall asleep (rather than stay asleep) then more immediate release is needed, Circadin may be crushed to provide an immediate release profile. Where a patient has problems staying asleep but can't swallow a tablet whole, part tablets or very coarsely crushed tablets will retain some of the modified release profile. If Circadin® cannot meet the clinical need, for example where the patient cannot manage crushed or chewed tablets, the unlicensed product Melatonin oral solution 5mg/5ml may be prescribed. This is included in the unlicensed liquid formulations in the drug tariff (part VIIIIB) and therefore has set price regardless of supplier.
If the clinical circumstances require a different unlicensed melatonin formulation the specialist will retain prescribing as the hospital can purchase at a lower cost and patient is likely to require frequent specialist contact.

**Dose**
Initiate at 2mg 1-2 hours before bedtime.
Increase dosage according to response. Dose can be increased to 4-6mg daily after 1-2 weeks.
Maximum BNF-C dose 10mg
Circadin® may be crushed or chewed to give an immediate-release profile.
If the child wakes during the night, an extra dose of melatonin should not be given.

**Cautions**
Patients with epilepsy (increased seizure activity has been reported, but there is also anecdotal evidence that seizure activity improves as a result of improved sleep)
Lactose intolerance

**Contraindications**
Hypersensitivity to Melatonin or to any of the excipients. Pregnancy or breastfeeding.

**Side effects**
Melatonin is generally well tolerated in children, but long term side effects have not been evaluated. Adverse effects that have been reported rarely include: daytime drowsiness, headache, dizziness, a reduction in body temperature, transient depressive symptoms, mild tremor, mild anxiety, abdominal cramps, irritability, confusion, nausea and hypotension.
For a full list of adverse effects refer to the Summary of Product Characteristics.
Some have advised use with caution in children with epilepsy and monitoring of seizure frequency; in practice this has not been a problem.
Melatonin can safely be withdrawn suddenly without risk of adverse effects

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Frequency</th>
<th>Management</th>
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</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>Uncommon (more than 1 in 1,000 to less than 1 in 100 people might get these)</td>
<td>Simple analgesia (e.g. paracetamol). Refer back to psychiatric team if persistent or troublesome.</td>
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<tr>
<td>Abnormal dreams</td>
<td>Uncommon</td>
<td>No management concerns. Offer reassurance that memory of dreams has improved.</td>
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<tr>
<td>Nausea</td>
<td>Uncommon</td>
<td>Usually transient. Try taking melatonin with or after food.</td>
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<tr>
<td>Dizziness</td>
<td>Uncommon</td>
<td>Try not to change posture too quickly. Refer back to psychiatric team if persistent or troublesome.</td>
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<tr>
<td>Leukopenia</td>
<td>Rare (more than about 1 in 10,000 to less than 1 in 1000 people might get these)</td>
<td>Stop medicine refer back to specialist. No routine full blood count is recommended.</td>
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</table>

**Interactions**
There is limited data on drug interactions with melatonin.
In theory, the effects of Melatonin may be additive with other medicines that cause CNS depression e.g. antidepressants, antipsychotics, other hypnotics and sedating antihistamines Fluvoxamine: can significantly increase melatonin levels.
Warfarin: INR may be increased. Melatonin might also increase the anticoagulant effect of other drugs with anticoagulant or antiplatelet properties.
Herbal remedies with anticoagulant or antiplatelet (e.g. Ginkgo biloba, Ginseng) or sedative properties (e.g. St John’s Wort, Valerian) may also enhance the therapeutic and adverse effects of melatonin.
Immunosuppressive therapy: Melatonin can stimulate immune function and might interfere with immunosuppressive therapy.
Nifedipine: melatonin can increase BP and heart rate in patients treated with Nifedipine
Cimetidine: can increase melatonin levels
Ciprofloxacin and other quinolones: can increase melatonin levels

**Criteria for Use**
Second-line where non-pharmacological strategies have failed and underlying physical causes are managed.
Treatment should be initiated by or under the supervision of a specialist and transferred to GP for prescribing after one month

**Duration of treatment:**
Duration of treatment should be determined on an individual basis.
Treatment should be discontinued every 6 months to assess if it is still beneficial.
GPs should prescribe only 28 days at a time with a review date of every 6 months.

**RESPONSIBILITIES and ROLES**

<table>
<thead>
<tr>
<th>Specialist responsibilities</th>
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<tbody>
<tr>
<td>1. To assess the patient and establish the need for sleep onset treatment in neurodevelopmental disabilities.</td>
</tr>
<tr>
<td>2. Consider and discuss treatment options. This should include consideration of contra-indications, interactions and cautions, a discussion of the reasons for treatment, the possible adverse effects and the lack of information in relation to longer-term outcomes including effectiveness and adverse effects</td>
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<tr>
<td>3. To consider melatonin where non-pharmacological strategies have failed, and underlying physical causes are managed where they exist.</td>
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<td>4. To consider only where parents, carers or, where appropriate the patient, has completed a sleep questionnaire and sleep diary highlighting problems with sleep latency.</td>
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<td>5. Provide verbal and written information to the parents, carers, and where appropriate the patient, and answer their questions about melatonin.</td>
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<td>6. Explain to the patient / carer their roles as below, ensuring the patient/carer is aware of the need to review the melatonin every 6 months.</td>
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<td>7. Obtain written consent for the off label/unlicensed (dependant on preparation) prescribing of melatonin.</td>
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<td>8. Perform baseline checks of physical health (including height, weight)</td>
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<td>9. Initiate off label melatonin (Circadin®) 2mg prolonged release tablets or occasionally the unlicensed 5mg/5ml solution if unable to have tablets even when crushed or chewed.</td>
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<td>10. Assess and monitor the patient’s response to treatment and make dose adjustments where necessary.</td>
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<td>11. If treatment is ineffective and discontinued check for possible complications following discontinuation.</td>
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<td>12. For patients remaining under specialist care (e.g. those with ADHD) undertake any necessary monitoring at clinic appointments (six monthly when stable): including height and weight.</td>
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<td>13. Assess the continuing need for melatonin at 6 monthly review and consider stopping melatonin e.g. 14 day break every 6 months using an appropriate sleep monitoring tool, and advise GPs on this for patients discharged from specialist care.</td>
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<tr>
<td>14. Maintain good communication with the GP. A written letter should be sent to the GP after each clinic visit. Keeping the GP fully informed about the patient's condition and medication. The specialist will be available to answer queries from the GP and carers.</td>
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<tr>
<td>15. To take responsibility for stopping the melatonin or to agree aftercare when the patient reaches 18 years of age</td>
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**Monitoring requirements**

**By specialist if ADHD diagnosis, by GP if discharged from specialist care (non-ADHD)**

1. Monitor continued positive impact on sleep and review every 6 months by discontinuing the medicine to assess continued benefit.
2. Monitor weight and standard monitoring of growth and sexual development (this has been seen in animals but not in human use of melatonin).
3. Although leukopenia is a known (rare) side effect, regular FBCs are not specifically required.

**General Practitioner responsibilities**

1. Subsequent prescribing of melatonin as Circadin® or occasionally the unlicensed 5mg/5ml solution at the dose recommended once the treatment has been established, the patient stabilised and the care of the patient has been transferred and accepted.
2. For patients discharged from specialist care, (e.g. those not under specialist for ADHD) undertake any necessary monitoring including height and weight every 6 months.
3. Refer patients back to the specialist if there is delayed sexual development or failure to gain weight and height for the expected age and familial characteristics.
4. For patients no longer under specialist care, assess the continuing need for melatonin at least 6 monthly and consider stopping melatonin e.g. 14 day break using an appropriate sleep monitoring tool
5. Re-refer the patient or seek advice from the specialist if there are on-going sleep problems, side-effects or other difficulties
6. Advise patients still under specialist care to attend appointments (at least 6 monthly).
7. To report any adverse drug reactions to the specialist and to the Medicines and Healthcare Products Regulatory Authority (MHRA) as part of the Yellow Card Scheme. [https://yellowcard.mhra.gov.uk/](https://yellowcard.mhra.gov.uk/)

**Patient’s / Carer’s role**

1. Ask the specialist or GP for information, if he or she does not have a clear understanding of the treatment.
2. Share any concerns in relation to treatment with melatonin
3. Tell the specialist or GP of any other medication being taken, including over-the-counter products.
4. Read the patient information leaflet included with your medication and report any side effects or concerns you have to the specialist or GP

**BACK-UP ADVICE AND SUPPORT**

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<tr>
<th>Contact details</th>
<th>Specialist</th>
<th>Telephone No.</th>
<th>Email address:</th>
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<tbody>
<tr>
<td><strong>Specialist:</strong></td>
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<td><strong>Hospital</strong></td>
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<td><strong>Pharmacy:</strong></td>
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<td><strong>Out of hours</strong></td>
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<tr>
<td><strong>contact:</strong></td>
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**PRIMARY CARE COST INFORMATION**

- Circadin® (Flynn) 30-tab pack = £15.39 (BNF May 14)
- Melatonin 5mg/5ml oral solution 200ml = £100.41 (Drug Tariff May 14)
Melatonin – information for families

This page has information for families about melatonin, a medicine that is used to help children who have trouble sleeping.

What is melatonin?
Melatonin is a natural hormone we all have. It is made in the brain. It is produced at night and helps regulate our sleep pattern. It helps our body know when it’s time to go to sleep and when it’s time to wake up.
Melatonin medicines contain a man-made version of this hormone.
No company currently holds a UK license to supply melatonin to be given to children. Your specialist will have given careful consideration to prescribing it, and will discuss this fully with you.

Why has it been prescribed?
Melatonin is prescribed by specialist doctors to help children and young people who have problems sleeping, when other ways of trying to help them sleep have not worked. These other methods should not stop now, but should continue along with the melatonin treatment.

How should it be taken?
Melatonin should be taken at the dosage prescribed by the specialist / GP. It must not be changed without their advice. It should be taken as a single dose, 30 to 60 minutes before sleep time. If the child wakes during the night, do not give an extra dose of melatonin.

Does melatonin have any side effects?
Everyone reacts differently to medicines and will not necessarily suffer from any of the side effects mentioned here. The most common problem with melatonin is that it simply does not make the sleep any better. Other than this, side effects are fairly uncommon, but may include headache, dizziness and abnormal dreams. Other side effects may include restlessness, increased sweating, stomach pains, dry mouth. There are differing reports on the effect of melatonin in children who have epilepsy or asthma. Any child with epilepsy or asthma will be monitored very closely. If your child develops any worrying symptoms, please discuss them with your doctor.

Is it safe to take other medicines with melatonin?
It is safe for a child to take paracetamol in the dosage recommended for their age alongside melatonin. For most other medicines, there has been no study of using them with melatonin. If you are discussing other medicines for your child with any doctor or pharmacist, tell them that your child is taking melatonin.

How long should my child take melatonin for?
It is usually recommended to continue with melatonin for several months if it is found to be useful. Then you can discuss with your specialist or GP how best to reduce the dosage to see how your child sleeps without it.

Where can we get more information or ask questions about melatonin?
This brief leaflet covers only some aspects of treatment with melatonin. The specialist, who prescribed the melatonin, or other members of his /her team, will be pleased to discuss it further with you. They will answer any questions that you have, now or in the future.