Pharmacological Therapies Policy Practice Guidance Note
Melatonin in Paediatric Sleep Disorders – V03

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Pharmacological Therapies

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1. **Introduction**

1.1 Melatonin is a hormone produced by the pineal gland located in the brain. It is normally secreted at night and its main function is the regulation of circadian rhythm and sleep, playing an important role in setting the correct timing of sleep-wake cycles.

1.2 Synthesis and secretion of endogenous melatonin are stimulated by darkness and inhibited by light. The administration of exogenous melatonin has a rapid, transient, mild sleep inducing effect and it lowers alertness, body temperature and performance for about 3 to 4 hours after the administration of low doses.

1.3 Insomnia and other non-respiratory sleep disorders in children and adolescents are a widespread problem, with a higher prevalence in children with neurodevelopmental or psychiatric co-morbidities. Melatonin has been used to manage insomnia in children with conditions such as visual impairment, cerebral palsy, attention deficit hyperactivity disorder (ADHD) and autism on the advice of hospital specialists for several years.

1.4 Until 2008 melatonin was only available in the UK as an unlicensed medicinal product which could either be imported from outside the UK or manufactured within the UK under a specials license.

1.5 The imported unlicensed products are non-pharmaceutical grade products from the USA, where melatonin preparations are classed as food supplements. As such these products are not subject to the standards of Good Manufacturing Practice normal for UK pharmaceuticals.

1.6 Within the UK there are currently one or more manufacturers who produce melatonin preparations under a specials license in a variety of formulations.

1.7 In 2008, Lundbeck Limited, were granted a marketing authorisation for Melatonin 2mg modified release (MR) tablets (Circadin®). This product is licensed for use in for primary insomnia in patients aged over 55.

2. **Purpose**

2.1 This policy on pharmacological treatment is intended to standardise the prescribing of melatonin for sleep disorders in children and young people throughout Northumberland, Tyne and Wear NHS Foundation Trust (the Trust/NTW). It should provide a framework for all children and young people whether being treated as inpatients or at home in the community.

3. **Availability of a Melatonin Product with a UK Marketing Authorisation (license)**

3.1 Following the availability of a licensed modified release melatonin product, the Medicines and Healthcare Products Regulatory Authority (MHRA) have advised that licensed melatonin products should be used wherever possible.

- This includes off-label use of the licensed product
3.2 Melatonin MR 2mg tablets (Circadin) have been approved for use by the North of Tyne Area Prescribing Committee in insomnia associated with neurodevelopment brain disorders in children and young people.

3.3 The availability of a licensed melatonin product and information for primary care facilitate the repeat prescribing of melatonin by GPs after treatment has been initiated by an NTW specialist. See section 7 for further prescribing guidance.

3.4 It is recognised, however, that there may be individual patients for whom the licensed product cannot meet their clinical needs. In particular, there may be some need for alternative dosage forms, strengths, or for an immediate release product.

4. **Unlicensed Prescribing and the Use of Unlicensed Medicines**

4.1 Importation of unlicensed melatonin products will require prescribers to provide written details of the special clinical need to the importer for submission to the MHRA. Details will have to be provided with every order and not just the first occasion. Prescribers are advised to use either melatonin modified release 2mg tablets or a pharmaceutical grade unlicensed product prepared by a UK Specials manufacturer rather than the imported melatonin products.

4.2 Patients in general should be made aware that they may be prescribed an unlicensed medicine. Individual patients (and/or their parents/carers) should be given adequate information about any unlicensed medicines to ensure continuity of supply and appropriate awareness of problems that may be associated with their use.

4.3 When a medicine is prescribed for a patient outside the terms of its product licence, consideration should be given to advising the patient (and/or his/her parent/carer where appropriate) that some of the details in a manufacturer's patient information leaflet may not be appropriate.

4.4 This can be done by informing the patient that the treatment they are being prescribed is one that has been marketed for use in another condition and as a consequence some of the information in the leaflet supplied with the medicine may not be appropriate for them. If this unlicensed use is one that is commonly prescribed it may be helpful to give the patient an explanatory leaflet prepared specifically. The use of the medication should also be documented in the patient’s notes. (See Trust policy NTW(C)17 – Medicine Management practice guidance note, UHM-PGN 27 - Unlicensed Prescribing and the Use of Unlicensed Medicines)
5. **Indications**

5.1 Melatonin is used to facilitate the induction of sleep, and increase the duration of sleep in children and young people on the advice of an appropriate secondary care specialist in the following situations:

- Children and young people with neurological or behavioural disorders including:
  - Attention deficit hyperactivity disorder (ADHD)
  - Chronic sleep onset insomnia
- Neurodevelopment disabilities (e.g. involving delayed brain maturation, sensory dysfunction - especially visual and dysfunction of sleep centres)
- Treatment of children and young adults with chronic fatigue syndrome / myalgic encephalomyelitis who have sleep difficulties (as recommended in NICE clinical guideline no. 53).
- Prior to examinations such as a sleep encephalogram (EEG) in children and sedation prior to scans in paediatric oncology.

5.2 The use of melatonin for the above indications is unlicensed and it is usually used as a second or third line therapy where sleep problems are adversely affecting quality of life in those where other methods of management including non pharmacological treatments have failed to work, are not tolerated or are impracticable.

6. **Dosage**

6.1 For children aged from 1 month to 18 years an initial dose of 2 – 3mg is recommended.

6.2 Immediate release preparations should be taken 30 – 60 minutes before bedtime and MR tablets should be given after food, 1 – 2 hours before bedtime.

6.3 In the absence of improvement after 1-2 weeks the dose can be increased to 4-6mg at night. The maximum dose is generally accepted to be 10mg but higher doses have been used. Treatment should be stopped in those that fail to demonstrate a response to the maximum dose.
7. Formulations

<table>
<thead>
<tr>
<th>Melatonin Products</th>
<th>Availability</th>
<th>Prescribing Status North of Tyne</th>
<th>Prescribing Status South of Tyne</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Product (where clinically appropriate)</td>
<td>Available as the licensed product Circadin®</td>
<td>Amber (Formal shared care guidance is available)</td>
<td>Green Plus</td>
</tr>
<tr>
<td>2mg modified release tablets*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternatives</td>
<td>Available as pharmaceutical grade unlicensed medicine from UK manufacturers e.g.: Penn Pharmaceuticals</td>
<td>Amber (Formal shared care guidance is available)</td>
<td>Amber (Formal shared care guidance is available)</td>
</tr>
<tr>
<td>1mg/ml oral solution*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imported Melatonin Products</td>
<td>Imported via IDIS or Mawdsley from USA</td>
<td>Red</td>
<td>Red</td>
</tr>
</tbody>
</table>

N.B. only the products marked * are included in the North of Tyne Formulary

Key

<table>
<thead>
<tr>
<th>Blue (NoT)</th>
<th>NTW specialist to initiate treatment and provide GP with information leaflet, GP may continue prescribing thereafter.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green Plus</td>
<td>NTW specialist to initiate treatment, GP may continue prescribing thereafter.</td>
</tr>
<tr>
<td>Amber</td>
<td>Drugs initiated by hospital specialist, but where continuing treatment by GPs may be appropriate under a shared care arrangement.</td>
</tr>
<tr>
<td>Red</td>
<td>Managed by NTW specialist only.</td>
</tr>
</tbody>
</table>

North of Tyne Shared Care Guidance (Amber) Available via this link: [http://medicines.necsu.nhs.uk/guidelines](http://medicines.necsu.nhs.uk/guidelines)

South of Tyne Shared Care Guidance for Unlicensed Melatonin (amber), licensed product is green plus
8. **Guidance for initiating melatonin therapy in new patients (children and young people of all ages)**

8.1 **First line:**

- Melatonin MR 2mg tablets at night
- Consider increasing the dose in the absence of improvement after 1 – 2 weeks to 4 – 6mg at night
- Usual maximum dose is 10mg though higher doses have been used
- **NB.** The licensed dose of this preparation for primary insomnia in patients aged over 55 is 2mg at night therefore the decision to increase the dose beyond 2mg in children and young people should be carefully considered

8.2 **Second line:**

- For patients who require a more immediate effect, the MR tablets should be crushed for administration. These can be administered with a spoonful of milk, yoghurt or jam
- Crushing destroys the coating on the tablets and removes their prolonged release properties
- Crushing the MR tablets is out with the terms of the product license (please refer to section 4 of this document for further information)

8.3 **Third line:**

- If the licensed form of melatonin MR (Circadin) cannot meet the clinical needs of the patient, the oral solution 5mg/5ml should be prescribed as this is the most cost-effective of the liquid formulations and its price is controlled by the drug tariff
- Again the initial dose should not exceed 2mg and any dose increase above this should be carefully considered and regularly reviewed

8.4 **Other Non-Formulary Preparation**

- Melatonin from Penn Pharmaceuticals or Special Products Ltd is available as an immediate release preparation. It is an unlicensed product but manufactured in the UK under a UK specials licence
9. **Prescribing for patients with Swallowing Difficulties or covert administration**

9.1 **First Line**
- The MR tablets should be crushed and administered with a spoonful of milk, yoghurt or jam

9.2 **Second line**
- The oral solution 5mg/5ml should be reserved for the few cases where crushing the tablets is not an option

- Refer to Trust policy NTW(C)17 – Medicine Management Practice Guidance Note, UHM-PGN-03 - Administration of Medicines for further advice regarding covert administration

10. **Special Warning and Precautions for Use**
- Driving or other activities that put the patient or others at risk should be avoided if the patient is affected by drowsiness
- Patients with hepatic impairment
- Patients with autoimmune diseases or taking immunosuppressants
- Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine

11. **Contraindications**
- Hypersensitivity to the active substance or to any of the excipients
- Children under 1 year of age
- Pregnancy
- Breastfeeding
- Sleep disturbance due to obstructive apnoea
12. Interactions

<table>
<thead>
<tr>
<th>Interacting substance</th>
<th>Effect of interaction</th>
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<tr>
<td>Fluvoxamine</td>
<td>Avoid concurrent use</td>
</tr>
<tr>
<td></td>
<td>Melatonin plasma concentrations are markedly increased via inhibited metabolism.</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Avoid concurrent use</td>
</tr>
<tr>
<td></td>
<td>Reduces efficacy of melatonin.</td>
</tr>
<tr>
<td>5 and 8-methoxypsoralen</td>
<td>Caution with concurrent use, increased melatonin plasma concentration.</td>
</tr>
<tr>
<td>CYP1A2 inhibitors</td>
<td></td>
</tr>
<tr>
<td>(e.g. ciprofloxacin, oestrogens (contraceptives and HRT), cimetidine)</td>
<td>Increased melatonin levels</td>
</tr>
<tr>
<td>CYP1A2 inducers</td>
<td></td>
</tr>
<tr>
<td>(e.g. Cigarette smoking, carbamazepine, rifampicin)</td>
<td>May reduce melatonin concentrations.</td>
</tr>
<tr>
<td>Other hypnotics and CNS depressants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caution with concurrent use. Melatonin may enhance the sedative properties of other drugs acting on the CNS (e.g. benzodiazepines and Z-drugs).</td>
</tr>
</tbody>
</table>

13. Adverse Effects

13.1 Melatonin is generally well tolerated and adverse reactions reported are at similar levels to those reported with placebo.

13.2 Tiredness, headaches, dizziness, pharyngitis, back pain, asthenia and irritability have been reported following its use. Other rare side effects include restlessness, confusion, increased heart rate, itching and nausea.

13.3 Discontinuation does not appear to be associated with withdrawal effects.

14. Monitoring

14.1 Treatment with melatonin should be initiated and supervised by a specialist.

14.2 If treatment is continued long-term, the need for on-going therapy should be reviewed every six months. Treatment should be stopped in patients who do not continue to benefit from its use.

14.3 Monitoring, particularly with regard to growth and pubertal/sexual development, is advised in children during long term administration, especially in those receiving melatonin for periods of a year or more.
15. Reporting errors and incidents involving melatonin

15.1 As with all medication incidents, these must be reported according to the Trust’s NTW(O)05 - Incident Policy.

15.2 All adverse reactions should be reported to the MHRA (preferably via the hospital pharmacy). This is particularly important with newly marketed medicines referred to as black triangle (▼) medicines, which will be under intense scrutiny by the MHRA.

16. References

- NTW(C)17 - Medicine Policy – Practice guidance note, UHM-PGN 27 - Unlicensed Prescribing and the Use of Unlicensed Medicines.
North of Tyne Area Prescribing Committee Shared Care Group. *Melatonin – Information for Primary Care.*
http://www.northoftyneapc.nhs.uk

NICE ESUOM2: Sleep disorders in children and young people with attention deficit hyperactivity disorder: melatonin Jan [ESUOM2: Sleep disorders in children and young people with attention...ESUOM2 Key points from the evidence](online; accessed 24 January 2014)