DRUG: Melatonin (Paediatrics)

Indication: Treatment of sleep disorders in children with visual problems and learning difficulties, cerebral palsy and autistic spectrum disorders. (unlicensed indication)

Licensing Information: Melatonin is unlicensed when used in children.

The MHRA have stipulated that licensed products should be used where possible even if it means using the product off label and outside the licensed indication. There may be some patients however for whom the licensed product is not suitable. A range of strengths and formulations of unlicensed melatonin are available from wholesalers/special-order manufacturers.

Modified release preparations:
- Melatonin M/R 2mg tablets pack size 30 (Circadin™) - are licensed in the UK for short term use in over 55s. These tablets must be swallowed whole.
- Melatonin M/R 3mg capsule (unlicensed) – capsule can be opened and given to children with swallowing difficulties. Available from Unlicensed Medicines in packs of 60.

Immediate release preparations:
If an immediate release preparation is required then it is preferable to use a product licensed within the EU.

- Melatonin tablets 2mg and 3mg pack size 60 (Bio-melatonin™) manufactured by Pharma Nord™ – are licensed in the EU. These tablets can be crushed and mixed with water if there are swallowing difficulties. In hospital these can be ordered direct from Pharma Nord (tel 01670 534901). In community they must be ordered through Phoenix or Quantum (tel 0800 043 9372).

An oral solution is also available but is more expensive

Other unlicensed immediate release preparations in various strengths are available and manufactured to good manufacturing standards under a ‘specials’ license in the UK e.g. from Penn pharmaceuticals (tel 01495 711222) and Special Products Ltd (01483 736950)

Formulations:
- Melatonin modified release 2mg tablets (Circadin™)
- Melatonin modified release capsules 3mg
- Melatonin immediate release tablets 2mg and 3mg (Pharma Nord)
- Melatonin immediate release capsules: 1mg, 2mg, 3mg and 5mg,
- Melatonin 1mg/1mL oral solution sugar free (Specials Products Ltd) - currently lowest cost liquid to the NHS
Available from various unlicensed UK specials and imports. See above for licensing information.

**Dosage & administration:**

- **Problems with sleep initiation:** standard release melatonin is used in children who have problems with sleep initiation. The starting dose is usually 1mg to 2mg given 30-60 minutes before bedtime. If there is no response or insufficient response after a minimum of seven days then the dose can be increased by 1mg or 2mg increments. The dose can be increased up to a maximum dose of 10mg. See licensing information for products available.

- **Problems with sleep maintenance/fragmental sleep and/or early morning awakening:** if there is a significant problem with sleep maintenance then controlled release melatonin will be used in the first instance. The licensed preparation (Circadin® - melatonin MR tablet 2mg) is used first line, 2mg given 1 – 2 hours before bedtime. In patients with swallowing difficulties, the unlicensed modified release capsules may be opened and the contents sprinkled on cold food e.g. spoonful of yoghurt. The contents of the capsule should not be mixed with liquids or hot food as this can cause dissolution of the beads and the slow release properties will be lost. The dose can be increased up to a maximum dose of 10mg.

**Contraindications & Warnings:**

- Contraindicated if there is hypersensitivity to the active substance or to any of the excipients.
- Use with caution in patients with liver disease, renal impairment, a history of cerebrovascular disease or a history of neurological disorders or depression.
- Manufacturer states to avoid in autoimmune disease as lack of information on use
- Care in patients with epilepsy as increased seizure activity reported rarely in epileptic patients.
- Lapp lactase deficiency for formulations containing lactose

**Interactions:**

- **Nifedipine** - melatonin may reduce effect of nifedipine on blood pressure. Mechanism is unknown and clinical relevance is probably minor
- **Warfarin** - INR may be raised or lowered when melatonin is prescribed with warfarin. Mechanism is unknown
- **CYP1A2 inhibitors (eg fluvoxamine, ciprofloxacin and other quinolones, oral contraceptives, methoxyssoralen and cimetidine)** – have the potential to increase melatonin levels. BNF advises to avoid fluvoxamine
- **CYP1A2 inducers (eg carbamazepine, rifampicin, smoking)** - have the potential to decrease melatonin levels
- Other hypnotics and CNS depressants: melatonin may enhance the sedative properties of other drugs acting on the CNS eg. benzodiazepines
<table>
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<tr>
<th>Adverse Effects:</th>
<th>For full list see SPC at <a href="http://www.medicines.org.uk/EMC">www.medicines.org.uk/EMC</a> and BNF for children</th>
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<tr>
<td>• <strong>Cardiovascular</strong>: tachycardia has been reported</td>
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<tr>
<td>• <strong>CNS</strong>: reports of headache, dizziness, increased irritability, restlessness and confusion. Increased seizure activity reported rarely in epileptic patients.</td>
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<tr>
<td>• <strong>Gastrointestinal</strong>: occur less commonly but include abdominal pain, dry mouth and nausea</td>
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<th>Responsibilities of the specialist initiating treatment:</th>
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<td><strong>General</strong>:</td>
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<td>• To assess and monitor the disease response throughout treatment with melatonin. The BNF for children advises that the need to continue melatonin therapy should be reviewed every 6 month.</td>
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<td>• To ensure that the patient/parent/carer has received counselling and understands the therapy, its benefits, limitations, continued monitoring (where applicable), adverse effects, and is aware of actions to take if adverse effects are suspected.</td>
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<td>• Inform the GP of the information provided to the patient.</td>
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<td>• To review the patient at agreed intervals and copy all relevant results to the GP.</td>
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<td>• Carry out disease monitoring.</td>
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<tr>
<td>• Formally hand over to GP by letter and patient informed - send a copy (either electronically or paper copy) of the shared care guideline to the GP and ask whether they are willing to participate in shared care.</td>
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<td><strong>Prescribing</strong>:</td>
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<tr>
<td>• Initiate treatment and provide at least 28 days supply. The GPs will be typically asked to take up prescribing of melatonin once response to treatment has been established and the child is on a stable dose.</td>
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<td>• Prescribe melatonin by brand name e.g. Circadin, Biomelatonin or Penn pharma melatonin.</td>
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<td><strong>Disease &amp; drug monitoring</strong>:</td>
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<td>• Discuss shared care arrangement with patient/parent/carer.</td>
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<td>• Support and advise GPs as required.</td>
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<tr>
<td>• Assess response to treatment and initiate any dose changes as clinically appropriate including discontinuation of treatment.</td>
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<tr>
<td>• To identify adverse effects if the patient presents with any signs and liaise with the hospital specialist where necessary. To report adverse effects to the specialist and where appropriate to the Commission on Human Medicines/MHRA (Yellow Card scheme).</td>
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<th>Responsibilities of other General and Prescribing:</th>
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<td>• To reply to the request for shared care within 2 weeks of receipt of the</td>
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prescribers (GP):

- Consult the consultant letter.
- Prescribe as recommended by the specialist. The GPs will be typically asked to take up prescribing of melatonin once response to treatment has been established and the child is on a stable dose.
- Notify consultant if treatment with melatonin is discontinued.
- Ensure there are no drug interactions or contra-indications with any other medications initiated in primary care.

Disease & drug monitoring:

- There is no routine blood monitoring required. GP to monitor for side effects, drug interactions etc.
- Urgent drug discontinuation/ referral to specialist as clinically appropriate.
- To stop treatment on the advice of the specialist.
- To refer back to the specialist if the patient’s condition deteriorates.
- To identify adverse effects if the patient presents with any signs and liaise with the hospital specialist where necessary. To report adverse effects to the specialist and where appropriate to the Commission on Human Medicines/MHRA (Yellow Card scheme).

Responsibilities of the Patient / Carer:

General:

- Ensure they have a clear understanding of the treatment.
- Take/give melatonin as directed.
- Report any possible side effects to their GP.
- Ensure they have an adequate supply of medication.
- Attend appointments including those for routine tests/investigations.
- Check with health care professional before purchasing herbal products as melatonin may theoretically increase the risk of bleeding when taken with herbs that have an affect on clotting and may have an additive sedative effect when taken with herbs that have sedative properties.

Disease & drug monitoring:

As above – contact GP or initiating team if side effects develop (see adverse effects) and attend appointments including those for routine blood tests/investigations.

Communication:

Specialist to GP:

- The specialist will inform the GP when they have initiated melatonin and when there are any subsequent changes in treatment – standard clinic letter.
- Send a copy (either electronically or paper copy) of the shared care guideline to the GP and ask whether they are willing to participate in shared care.
- Inform the GP of the information provided to the patient.

GP to Specialist:

- To reply to the request for shared care within 2 weeks of receipt of the
consultant letter.
• Irrespective of whether you accept prescribing responsibility or not, you should inform the consultant of relevant medical information regarding the patient and changes to the patient’s medication regime irrespective of indication.
• Notify consultant if treatment with melatonin is discontinued.

Contact names & details:
If you have any concerns regarding individual patients, see consultant letter for medical contact details or contact one of the following:

Please refer to Clinic letter for details of Consultant and contact via switchboard.
York 01904 631313
Scarborough 01723 368111

Cost:
Several melatonin preparations are unlicensed “specials” which are not listed in the Drug Tariff and therefore are subject to cost variation in primary care. Every effort should be made to select a suitable product representing the best value to the NHS.
The following prices for primary care are correct at the time of writing:

**Drug Tariff listed products Jan 2015:**
Melatonin 2mg modified-release tablets (Circadin) – 30 tablets £15.39
Melatonin 1mg/1mL oral solution sugar free – 200mL £89.99.
Other liquid formulations are available but at greater NHS cost.

The following products are not listed in the Drug Tariff, liaise with the local pharmacy and/or CSU Medicines Management Team for up to date advice on local choice/costs.

Melatonin 2mg tablets (Pharma Nord) -60 £16.41
Melatonin 3mg tablets (Pharma Nord) -60 £16.92

References:
• BNF for Children 2014-15
• Circadin SPC last updated 2.9.13
• Stockley drug interactions accessed 12.1.15

This information is not inclusive of all prescribing information and potential adverse effects. Please refer to the SPC (data sheet) or BNF for further prescribing information.