

SHARED CARE PROTOCOL: MELATONIN

NHS GREATER GLASGOW AND CLYDE

NB: This document should be read in conjunction with the current Summary of Product Characteristics (SPC) where appropriate.

DRUG AND INDICATION:

Generic drug name:	MELATONIN
Formulations:	3mg tablets (Bio-Melatonin®) 2mg modified-release tablets (Circadin®) 1mg/ml oral solution – if crushed tablets not tolerated /not appropriate
Intended indication:	Sleep aid for children over 2 years of age with neurodevelopmental disorders and chronic sleep disturbance
Status of medicine or treatment:	Bio-melatonin® - Licensed indication for licensed medicine in EU but not in the UK. Circadin® is licensed in the UK for those aged 55yrs and over. Oral solution is unlicensed in the UK but manufactured as a 'special' by various manufacturers including Rosemont, Mawdsleys

RESPONSIBILITIES OF ACUTE CARE/SPECIALIST SERVICE

- To assess the suitability of patients for treatment.
- Undertake any baseline investigations/monitoring.
- Initiate prescribing of melatonin, monitor response and adjust dose until stabilised.
- To assess and monitor the patient's response to treatment and to check for possible complications, with discontinuation of the treatment if ineffective and dose adjustment if necessary.
- To advise the GP regarding the periodic discontinuation of melatonin to determine its on-going need e.g on the length and frequency of treatment breaks, or how to improve efficacy in children who are slow metabolisers.
- To advise patients when treatment withdrawal should be considered.
- To report any suspected adverse events to the MHRA.

Acute care/specialist service will provide the GP with:

- A letter including diagnostic information and details of the dose and preparation of melatonin to prescribe, and including the duration of treatment before specialist review, if appropriate.
- Written report of outpatient consultations, ideally within 14 days of seeing the patient.

Acute care/specialist service will provide the patient/ carer with relevant drug information to enable:

- Informed consent to therapy.
- Understanding of potential side effects and appropriate action.
- Understanding of the role of sleep monitoring.

RESPONSIBILITIES OF PRIMARY CARE (GENERAL PRACTITIONER):

- To prescribe treatment following stabilisation of dose in collaboration with the Specialist.
- To ensure that patients primary care medication records are kept updated to reflect advice from specialist service e.g. dose adjustments.
- Manage any adverse effects or refer to specialist service as outlined in this protocol.

RESPONSIBILITIES OF PATIENT/PARENT/CARER:

- To attend hospital and GP clinic appointments and bring sleep monitoring booklet (if issued).
- Failure to attend appointments will result in medication being stopped.
- To report adverse effects to their specialist or GP.

ADDITIONAL RESPONSIBILITIES:

DOCUMENT PRODUCED BY: DR A RENNIE, DR G AKRAM AND DR A ADDO
DOCUMENT APPROVED BY: PRESCRIBING INTERFACE SUBCOMMITTEE OF ADTC
DATE APPROVED: JUNE 2016
PLANNED REVIEW DATE: JUNE 2018

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- Any serious reaction should be reported to the Commission of Human Medicines (CHM) by whoever they are highlighted to. Use the Yellow Card System to report adverse drug reactions- <http://yellowcard.mhra.gov.uk/>

CAUTIONS:

Melatonin may cause drowsiness- it should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety

Cautions for melatonin 3mg tablets (Bio-Melatonin®):

- Must be used under medical supervision. Caution should be exercised in patients with epilepsy, autoimmune, renal or hepatic disorders.

Cautions for melatonin 2mg MR tablets (Circadin®):

- No clinical data exist concerning the use of Circadin in individuals with autoimmune diseases. Therefore Circadin is not recommended for use in patients with autoimmune diseases.
- Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Cautions for melatonin 1mg/ml oral solution

- Nothing specific from 'Specials' manufacturers.
- Caution in renal impairment. Avoid in hepatic impairment.

CONTRAINDICATIONS:

- Hypersensitivity to the active substance or to any of the excipients.
- Autoimmune disease

TYPICAL DOSAGE REGIMENS:

Dosage regimen for melatonin 3 mg tablets (Bio-Melatonin®)

Route of administration:	Oral – may be crushed.
Recommended starting dose:	One tablet to be taken 1 hour before desired sleep time.
Titration of dose:	Increase to 6 mg depending on response after 7 – 14 days
Maximum dose:	12 mg daily but additional benefits from doses above 6 – 9 mg are uncertain
Adjunctive treatment regimen:	Sleep hygiene (advice)
Conditions requiring dose adjustment:	Non response (delayed time to sleep onset, disturbed sleep, early morning awakening)
Usual response time:	7 days
Duration of treatment	Indefinite- some children who are slow metabolisers may benefit from a short break since they may have daytime build up of melatonin making it less effective at night-time.

Dosage regimen for melatonin 2 mg MR tablets (Circadin®)

Route of administration:	Oral – to be taken whole.
Recommended starting dose:	One tablet to taken 1 hour before desired sleep time after food
Titration of dose:	Increase by 2 mg depending on response every 7-14 days
Maximum dose:	8 mg
Adjunctive treatment regimen:	Sleep hygiene (advice)
Conditions requiring dose adjustment:	Non response (delayed time to sleep onset, disturbed sleep, early morning awakening)
Usual response time:	7 days
Duration of treatment	Indefinite- some children who are slow metabolisers may benefit from a short break since they may have daytime build up of melatonin making it less effective at night-time.

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Dosage regimen for melatonin 1mg/ml oral solution

Route of administration:	Oral
Recommended starting dose:	2- 3 ml (e.g 2 – 3 mg) taken as a single dose an hour before desired sleep time.
Titration of dose:	Increase to 4- 6 mg depending on response after 7 – 14 days
Maximum dose:	10 mg daily but additional benefits from doses above 6 – 9 mg are uncertain
Adjunctive treatment regimen:	Sleep hygiene (advice)
Conditions requiring dose adjustment:	Non response (delayed time to sleep onset, disturbed sleep, early morning awakening)
Usual response time:	7 days
Duration of treatment	Indefinite- some children who are slow metabolisers may benefit from a short break since they may have daytime build up of melatonin making it less effective at night-time.

All dose adjustments to be performed by acute/specialist services with changes notified in a letter to the GP.

SIGNIFICANT DRUG INTERACTIONS:

- Increased sedative effect when given with antipsychotics and other hypnotics.
- Interaction of melatonin with selective serotonin re-uptake inhibitors has been observed.
- Melatonin may potentiate the effectiveness of warfarin or other oral anticoagulants, and may increase the effectiveness of monoamine oxidase inhibitors.
- Melatonin may reduce the effectiveness of nifedipine and other calcium-channel blockers.

UNDESIRABLE EFFECTS:

- Melatonin is generally well tolerated with only a few adverse side-effects having been reported. Most commonly reported side-effects include headaches, nausea and drowsiness.

ADR details	Management of ADR
Uncommon: Irritability, nervousness, restlessness, insomnia, abnormal dreams, anxiety, migraine, lethargy, psychomotor hyperactivity, dizziness, somnolence	▪ Refer to specialist service and if ADR is clinically significant discontinue medicine prior to referral.
Uncommon: Dermatitis, night sweats, pruritus, rash, pruritus generalised, dry skin	▪ Refer to specialist service and if ADR is clinically significant discontinue medicine prior to referral.
Uncommon: Hypertension	▪ Refer to specialist service and discontinue medicine prior to referral.
Uncommon: Abdominal pain, abdominal pain upper, dyspepsia, mouth ulceration, dry mouth, hyperbilirubinaemia	▪ Refer to specialist service and if ADR is clinically significant discontinue medicine prior to referral.

BASELINE INVESTIGATIONS / MANAGEMENT:

- Height and weight.
- Clinicians should determine if appropriate sleep hygiene measures have been used prior to initiating prescribing of melatonin.

MONITORING (PRIMARY CARE):

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- All routine monitoring relating to response is undertaken within the specialist service
- If the GP notes any concerns regarding height, weight or pubertal development, they should refer to the Specialist.

MONITORING (ACUTE SECTOR):

- The following monitoring should be undertaken by Acute/Specialist services

Monitoring Parameters	Frequency	Laboratory results	Action to be taken
Height & weight	Annual	N/A	Further assessment if abnormal parameters
Pubertal development	As required	N/A	Consider stopping melatonin. Investigate further as required.

PHARMACEUTICAL ASPECTS:

Melatonin Preparations: There are many different strengths and formulations available; however the majority of these are unlicensed. Currently, there are only two products which meet the Medicines and Healthcare Products Regulatory Agency (MHRA) specifications. Upon receipt of a GP10 prescription, only these two products are likely to be dispensed from Community Pharmacies. Both products are included in the NHS GG&C paediatric formulary. The simultaneous use of the standard and modified release preparations may be useful in some children.

Melatonin standard release: Bio-Melatonin® tablets, 3mg tablets, 60 tablets per pack.

- The tablets may be crushed and mixed with small amounts of food or liquids such as water, juice or milk. (Can then be administered via a NG tube or gastrostomy if required).
- The tablets are sugar, yeast and gluten free.

Melatonin sustained release: Circadin 2mg tablets, 21 tablets per pack.

- The tablets must be swallowed whole.
- Can be useful for children who have a fragmented sleeping pattern and wake up through the night.

Melatonin oral solution 1 mg / ml (immediate release): 200 ml ('Special' unlicensed product).

- Flavoured solution, likely to be sweetened and contain ethanol as excipient.

To avoid delays, it is advised that other strengths and preparations of melatonin ARE NOT prescribed.

COST:

PLEASE NOTE: All medicines included in a shared care protocol that meet the criteria for a "high cost expensive medicine" and are prescribed in accordance with the shared care protocol are automatically accounted for in the "high cost/ expensive medicines list" for budget-setting purposes. No additional action is therefore required by GPs to request funding. For those medicines which are the subject of a shared care protocol but which do not meet the high cost expensive medicines criteria, transfer of prescribing costs will be considered if this is appropriate.

This is difficult to define as various brands are currently dispensed, some of which are imported, and some bought via Specials manufacturers whilst others are branded licensed products. Prices range from £60 for 60 tablets to £97 for 200ml oral liquid. (Scottish Drug Tariff, March 2016)

INFORMATION FOR COMMUNITY PHARMACIST:

Circadin® is a licensed medicine in the UK and should be available from most wholesalers.

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Melatonin 1mg/ml oral solution- can be ordered as a 'Special' unlicensed product- for reimbursement the GP10 prescription **must** be endorsed to indicate it is being supplied 'under Section 7 of the Drug Tariff'.

Bio-Melatonin® tablets are licensed as a medicine elsewhere within the EU, but not within the UK. Obtaining this preparation via wholesalers will often incur additional costs, and currently it is recommended that the medicine is obtained directly from the manufacturer (Pharma Nord Specials (UK) Ltd). Their contact details are as follows:

Pharma Nord Specials (UK) Ltd
Telford Court
Morpeth
Northumberland
NE61 2DB
Tel: 01670 534901
Fax: 01670 534902
Email: specials@pharmanord.com

ACUTE CARE/SPECIALIST SERVICE CONTACT INFORMATION:

Name	Designation	Acute Site	Department phone number
Dr Alison Rennie	Consultant Paediatrician	Specialist Children's Services	0141 227 7650
Dr Ama Addo	Consultant Psychiatrist	RHC	0141 232 1956
Dr Gazala Akram	Specialist Pharmacist (Psychiatry)	RHC	0141 452 4535 (page 8417)

SUPPORTING DOCUMENTATION:

- An information leaflet for parents regarding melatonin (Royal College of Paediatrics & Child Health approved) is available at <http://www.medicinesforchildren.org.uk/search-for-a-leaflet/melatonin-for-sleep-disorders/> Consultants, GPs or community pharmacists are able to print this leaflet in PDF format.
- Dear GP letter.