SHARED CARE AGREEMENT: MELATONIN (CHILDREN)

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 immediate release tablets 2mg modified-release tablets 1mg/ml oral solution – if crushing tablets is not an option or is unsuitable.
Intended indication:	Sleep aid for children over 2 years of age with neurodevelopmental disorders **and** chronic sleep disturbance
Status of medicine or treatment:	An NHS GGC Paediatric Formulary medicine Licensed products are available for the treatment of jet lag and sleep disturbance in adults but their use in children for sleep management represents off-label prescribing.

RESPONSIBILITIES OF ACUTE CARE/SPECIALIST SERVICE

- To assess the suitability of patients for treatment.
- To undertake any baseline investigations and monitoring.
- To initiate prescribing of melatonin, monitor response and recommend any dose adjustments as necessary.
- To assess and monitor the patient's response which may require adjustments in dose, to check for possible complications, with discontinuation of treatment if it is ineffective.
- To advise the parent / carer / patient 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 may be slow to metabolise.
- 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, including the duration of treatment before Specialist review, if appropriate.
- A written report of outpatient consultations, ideally within 14 days from when the consultation occurred.

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

- Informed consent to therapy.
- Understanding of potential side effects and appropriate action.
- Understanding of the role of sleep hygiene and its monitoring.
- Understanding of changes in formulation if required.

RESPONSIBILITIES OF PRIMARY CARE (GENERAL PRACTITIONER):

- To prescribe treatment following stabilisation of the dose in collaboration with the specialist.
- To ensure that the patient's Primary Care medication records are updated to reflect advice from specialist services e.g. dose adjustments.
- Manage any adverse effects or refer to specialist services as outlined in this agreement.

RESPONSIBILITIES OF PATIENT / PARENT / CARER:

- To attend hospital and GP clinic appointments and bring the sleep monitoring booklet (if issued) to appointments.
- Failure to attend appointments may result in the medication no longer being prescribed.
- To report adverse effects to their Specialist or the GP.

ADDITIONAL RESPONSIBILITIES:

- Any serious reaction should be reported to the MHRA by whoever they are highlighted to. Use the Yellow Card System to

report adverse drug reactions- http://yellowcard.mhra.gov.uk/

CAUTIONS:

Melatonin causes drowsiness- it should be used with caution if the effects of drowsiness are likely to cause a risk to safety
Caution required in renal and hepatic impairment- Avoid in severe impairment.
Caution should be exercised in patients with epilepsy and autoimmune diseases.

Melatonin immediate release 3mg tablets
No additional cautions.

Melatonin modified release 2mg tablets

- Should be swallowed whole and not be broken, crushed or chewed as this affects the prolonged release properties.
- Melatonin modified release tablets are 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.

Melatonin 1mg/ml oral solution

- The licensed oral solution has a higher than acceptable content of propylene glycol, making this product less suitable for children under 5 years. *It is suggested that this detail be checked prior to dispensing.*

CONTRAINDICATIONS:

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

TYPICAL DOSAGE REGIMENS:

Dosage regimen for melatonin 3 mg immediate release tablets

Route of administration:	Oral – tablets swallowed or crushed (may be mixed with small amount of water).
Recommended starting dose:	One tablet (3mg) 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 in treatment (to avoid elevated plasma levels during the day making it less effective at night-time).

Dosage regimen for melatonin 2mg modified release tablets

Route of administration:	Oral – to be taken whole.
Recommended starting dose:	One tablet (2mg) to be 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 in treatment (to avoid elevated plasma levels during the day making it less effective at night-time).

Dosage regimen for melatonin 1mg/ml oral solution (recommended in over 5 years only)

Route of administration:	Oral
Recommended starting dose:	2- 3 ml (i.e. 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 in treatment (to avoid elevated plasma levels during the day 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.
- Melatonin is metabolised via the CYP1A enzymes CYP 450 so there is increased potential for interactions to occur with other medicines that are metabolised via the CYP 450 mechanism e.g. SSRIs, oestrogens, cimetidine, nifedipine and other calcium-channel blockers, warfarin or other oral anticoagulants - **THIS LIST IS NOT EXHAUSTIVE.**
- Beta-blockers may suppress the night-time release of endogenous melatonin and thus should be administered in the morning.

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. Melatonin may increase seizure frequency in patients with epilepsy.

Side effects	Management
Uncommon: Irritability, nervousness, restlessness, abnormal dreams, anxiety, migraine, lethargy, psychomotor hyperactivity, dizziness, somnolence, dermatitis, night sweats, hypertension, pruritus, rash, dry skin	Refer to specialist service and if serious / clinically significant discontinue medicine prior to referral.
Rare: leucopenia, altered mood, aggressive behavior, syncope, palpitations, hot flushes, reduced visual acuity mouth ulceration, dry mouth,	Refer to specialist service and discontinue medicine immediately.

BASELINE INVESTIGATIONS / MANAGEMENT:

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

MONITORING (PRIMARY CARE):

- 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.
Clinical efficacy	Annual	N/A	Treatment is reviewed annually and discontinued if not effective. On discharge from SCS a final review is undertaken with a view to stopping melatonin where possible.

PHARMACEUTICAL ASPECTS:

Melatonin immediate release tablets 3mg.

- Film coated tablets
- May be crushed if required and are preferred to the use of liquid formulations. (Can then be administered via a NG tube or gastrostomy if required – this reflects local practice and is an unlicensed use).

Melatonin modified release 2mg tablets, 21 tablets per pack.

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

Melatonin oral solution 1 mg/ml:

- This product should only be considered if crushing licensed 3mg standard release tablets is unsuitable. This formulation contains higher than recommended amounts of the excipient propylene glycol, making it less suitable for use in children under 5 years of age (see Medicines Information Briefing What are the implications of the new licensed melatonin preparations?)

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

Unlicensed Melatonin Preparations: There are many different unlicensed strengths and formulations available. Unlicensed melatonin products should only be used where there is a 'special clinical need'. The prescriber will require to provide a letter of clinical need for every prescription for unlicensed melatonin (See MHRA statement here).

COST:

Prices range from £15.39 for 30 X 2mg modified release tablets to £14.95 for 30 X 3mg immediate release tablets. Oral solution (1mg/ml, 150ml) is £130. (British National Formulary, accessed January 2020 and Scottish Drug Tariff October 2020).

INFORMATION FOR COMMUNITY PHARMACIST:

Melatonin 3mg immediate release tablets, melatonin 2mg modified release tablets and the 1mg/ml oral solution should be available for ordering from regular wholesalers.
Other products may require a *letter of clinical need* from the prescriber.

ACUTE CARE/SPECIALIST SERVICE CONTACT INFORMATION:

Name	Designation	Acute Site	Department phone number
Dr Alison Rennie	Consultant Paediatrician	Specialist Children's Services	0141 277 7475
Dr Laura Somerville	Consultant Paediatrician	Specialist Children's Services	0141 207 7100
Stephen Bowhay	Lead Clinical Pharmacist	Royal Hospital for Children	0141 451 5710
Dr Helen Tindle	Consultant Psychiatrist	Royal Hospital for Children	0141 232 1956
Dr Gazala Akram	Specialist Pharmacist (Psychiatry)	Royal Hospital for Children	0141 452 4551

SUPPORTING DOCUMENTATION:

- A Royal College of Paediatrics & Child Health approved information leaflet regarding melatonin (is available at https://www.medicinesforchildren.org.uk/melatonin-sleep-disorders)
- MHRA Hierarchy – Appendix 2 Guidance on the hierarchy for the use of unlicensed medicines
- West Midlands Medicines Information Service - What are the implications of the new licensed melatonin preparations?