Melatonin Prescribing Support Information – Children & Young People

This information is provided to support primary care clinicians prescribing melatonin for children and young people in Bedfordshire, Luton and Milton Keynes ICS.

Category	Melatonin is a hormone produced by the pineal gland in the brain and helps to regulate the sleep-wake cycles
Therapeutic indications	Diagnosis of a sleep disorder in children and young people made by a specialist in paediatrics, CAMHS and Learning Disabilities (LD). For use in children of at least 3 years of age with neurodevelopmental conditions (e.g. autism, ADHD) and/or intellectual disability, where symptoms of sleep disturbance have been present for at least six months or sleep disturbance is so severe that it is causing significant family disturbance. This includes use in children with chronic sleep disturbances, chronic fatigue syndrome, cerebral palsy and visual impairment who would benefit from melatonin to help with sleep regulation. For children aged 1-2 years, melatonin should be used by exception due to the lack of sufficient evidence supporting its safety and efficacy in this age group. Use of melatonin should only be considered after excluding other underlying conditions that can cause sleep disturbance.
Place in therapy	First line medication where sleep hygiene measures, behavioural, parental and psychological interventions have been ineffective.
Pharmaceutical form / product choice	Immediate release (IR) tablets Modified release (MR) tablets Oral liquid 1mg/ml See BLMK formularies for current formulary choices: https://www.bedsformulary.nhs.uk/ https://www.formularymk.nhs.uk/ The licensed indication may differ depending upon the product that is prescribed. Licensed doses, age range and disease indication can vary between the different preparations, therefore use of some of the recommended formulary products may be off label. The decision to use IR or MR tablets will be made by the specialist and is determined by the child's sleep profile, usually:

Release profile	**Sleep profile**
Intermediate release (IR)	Problems with sleep initiation
Modified release (MR)	Problems with sleep duration e.g. frequent night waking or disrupted sleep

This information does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it. Please see BNF & SPC for comprehensive information.

The following organisations contribute to and participate in the BLMK APC – Bedfordshire, Luton and Milton Keynes Integrated Care Board; Bedfordshire Hospitals NHS Foundation Trust; Cambridgeshire Community Services NHS Trust; Central and North West London NHS Foundation Trust; East London NHS Foundation Trust; Milton Keynes University Hospital NHS Foundation Trust

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Formulary status	Amber SpIS – Specialist to initiate and stabilise medicine prior to continuation in Primary Care
Responsibilities	GPs/primary care prescribers may prescribe melatonin following initiation and stabilisation by the specialist. The specialist will recommend, initiate and prescribe the initial supply of 28 days of melatonin, and up to the first three months if needed. The specialist should confirm that the patient is optimised on the chosen medication with no further changes anticipated in the immediate future.
Dosing Advice	**Initial stabilisation (IR or MR)**: oral starting dose is usually 1mg at night, 30-60 minutes before bedtime. Dose adjustments are made in increments of 1-2mg. Intervals of dose increase depend upon response. Stable dose can be reached at one month of starting the melatonin if child shows a response to 2mg dose. Recommended maximum dose is 10mg/day. **Maintenance dose (IR or MR):** 2-10mg at night, taken 30-60 minute before bedtime. **Conditions requiring dose adjustment:** Change in clinical presentation impacting sleep. Puberty development and growth.
Duration of treatment	The specialist should consider stopping melatonin if there is no clinical response after three months. Prescribers are required to monitor sleep patterns and should review the need to continue treatment every 6-12 months and adjust doses as necessary. For many patients, the use of melatonin will be a medium term medication to support behavioural interventions. The specialist will then advise the Primary Care Prescriber on future management. It is unusual for a child to continue melatonin into adulthood. It is the responsibility of the referring specialist to decide if it is appropriate to continue for a specific individual. The specialist will then advise the Primary Care prescriber on future management.
Treatment breaks	Breaks from melatonin are advised for all children on melatonin to help optimise response, but in particular where the child/ young person is on a high dose (e.g. 8-10mg at night) to help reduce tolerance and allow for re-challenge if appropriate. Re-challenge can be done in either primary or secondary care. The specialist should consider a melatonin free trial at least annually to assess the continued need for treatment. The outcome of any treatment break must be recorded in the patient's notes. Not all children take melatonin every day and prescribing and use is based on the needs of the child. This means some children will take breaks on weekends and during holidays, as part of the treatment plan.
Discharge from specialist service	Patients may be discharged from the specialist service after 6 months if they are stable on treatment, only if there is no other clinical reason for the patient to remain under the care of the specialist. A clear plan will be provided to the primary care clinician including dose, intended duration and the need for treatment breaks. At any point, practices may refer back to the specialist service for additional support and advice.

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Special patient populations	**Renal impairment** • Caution should be used when melatonin is administered to patients with renal impairment. **Hepatic impairment** • *Immediate-release formulations:* avoid in moderate or severe impairment (risk of decreased clearance; limited information available). • *Modified-release tablets:* avoid (risk of decreased clearance; limited information available).
Contra-indications	• Hypersensitivity to melatonin or any excipients • Patients with autoimmune diseases or taking immunosuppressants. • Patients with severe renal impairment • Patients with moderate to severe hepatic impairment
Cautions (see SPC for full details)	• Drowsiness - driving or other activities that put the patient or others at risk should be avoided if the patient is affected by drowsiness. • Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take melatonin products that contains lactose. • Patients with renal or hepatic impairment (see also contraindications above). • Melatonin may worsen restless legs syndrome. • Patients with asthma. • Melatonin can affect serotonin levels and should be used with caution in conjunction with other serotonin related agents. • There is a known potential for melatonin to affect seizure control in patients with epilepsy hence monitoring of seizure frequency is advised. The effects on initiation and titration of melatonin in epileptic patients should be closely monitored. Melatonin has been reported to increase, decrease or have no effect on seizure frequency. Additionally poor sleep is known to worsen seizure control. • Limited data suggest that melatonin taken in close proximity to ingestion of carbohydrate-rich meals may impair blood glucose control for several hours. Melatonin should be taken at least 2 hours before and at least 2 hours after a meal; ideally at least 3 hours after meals by persons with significantly impaired glucose tolerance or diabetes
Adverse effects (see SPC for full details) **▼ drug – report suspected adverse effects to the MHRA**	Most side effects are transient and will pass after a few days. If side effects persist and are causing distress: In the first instance lower melatonin to previously tolerated dose; if this is not effective, it is advised to stop melatonin and contact the relevant specialist team for advice. The most frequently reported adverse effects are nausea, vomiting, headache, somnolence and fatigue. Additional adverse effects reported for melatonin include irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety, migraine, lethargy, psychomotor hyperactivity, dizziness, hypertension, abdominal pain, dyspepsia, mouth ulceration, dry mouth, abnormal liver function tests, weight gain, pruritus, rash, dry skin, hypersensitivity reactions, chest pain, malaise.

Pregnancy, lactation and fertility (see SPC for full details)	**Pregnancy** There are limited data from the use of melatonin in pregnant women. Exogenous melatonin readily crosses the human placenta. Animal studies are insufficient with respect to embryofoetal development. Melatonin is not recommended during pregnancy or in women of childbearing potential not using contraception. **Breast feeding** There is insufficient data on the excretion of melatonin / metabolites in human milk. Endogenous melatonin is secreted in human milk and the available data indicates that exogenous melatonin is most likely also excreted in human milk. Product manufacturers do not recommend use of melatonin while breast feeding. For additional support and advice on prescribing during pregnancy and while breast feeding see Perinatal Mental Health – Guidance for GPs. **Fertility** No adequate data on the effect of melatonin on human fertility are available. Animal studies are incomplete in terms of effects on fertility. High doses of melatonin and use for longer periods than indicated may compromise fertility in humans.

Interactions (see SPC for full details)	Melatonin is mainly metabolised by CYP1A enzymes. Interactions between melatonin and other active substances that affect CYP1A enzymes are therefore possible.
	
	CYP1A2 inhibitors may markedly increase the plasma concentrations of melatonin:
	• **Avoid** concomitant use with **fluvoxamine**.
	• **Caution** is advised in combination with the following (melatonin dose may need to be reduced):
	  ○ Oestrogens
	  ○ Quinolones
	  ○ Verapamil
	  ○ 5- or 8-methoxypsoralen (5 or 8-MOP)
	  ○ Cimetidine
	
	CYP1A2 inducers may decrease the plasma concentrations of melatonin and dose adjustment may be required (list is not exhaustive – see SPC for further information):
	• Carbamazepine, phenytoin, rifampicin, omeprazole
	• Cigarette smoking
	
	In addition, melatonin may affect the following:
	• Enhanced sedative effect of benzodiazepines and non-benzodiazepine hypnotics when used in combination with melatonin.
	• Melatonin may affect the anticoagulation activity of warfarin – monitor INR.
	• Alcohol should not be taken with melatonin, because it reduces the effectiveness of melatonin on sleep.
	• Melatonin may reduce the hypotensive effect of nifedipine.

Counselling points	• Emphasise the importance of good sleep hygiene (see resources below). • Take 30-60 minutes before bedtime. • Take the melatonin after food (melatonin should be taken at least 2 hours before and at least 2 hours after a meal; ideally at least 3 hours after meals by persons with significantly impaired glucose tolerance or diabetes).

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	• For children waking during the night, the same dose or a smaller dose can be repeated during the night (as prescribed by the specialist - to be communicated to the Primary Care Prescriber in writing). The patient/carer should be advised to report any of the following signs or symptoms, following initiation of melatonin, to their Primary Care prescriber without delay: • Hypersensitivity reaction • Abnormal dreams/ nightmares • Changes in mood and/ or mental state • Chest pains
Practical issues / additional information	Choice of melatonin product should be in accordance with agreed formulary choices. Care should be taken to select the correct formulation e.g. immediate release or modified release. Additional information: • For some brands of immediate release melatonin, the licensing covers the medicine being used in a crushed form (see formularies for details). • Melatonin 2mg MR tablets can be halved using a tablet cutter and the slow release characteristics will be retained. • NOTE: crushing a MR tablet will mean that it is no longer modified release. • Some use of melatonin in children and young people may be off-label – the specialist must ensure the patient/carer is aware of the off-label status (if applicable). Patient information leaflet on melatonin can be obtained from: Medicines for Children https://www.medicinesforchildren.org.uk/medicines/melatonin-for-sleep-disorders/
Sleep hygiene resources	https://www.nhs.uk/every-mind-matters/mental-health-issues/sleep/ https://www.nhs.uk/conditions/insomnia/ https://cks.nice.org.uk/topics/insomnia/management/managing-short-term-insomnia-less-3-months/#good-sleep-hygiene https://www.gosh.nhs.uk/conditions-and-treatments/procedures-and-treatments/sleep-hygiene-children/ https://www.headspace.com/sleep/sleep-hygiene https://thesleepcharity.org.uk/information-support/children/sleep-diary-for-kids/
References	1. Summary of product characteristics (accessed 22/10/24) Adaflex 2 mg tablet - Summary of Product Characteristics (SmPC) - (emc) Ceyesto 1mg/ml Oral Solution - Summary of Product Characteristics (SmPC) - (emc) Melatonin Mylan 2 mg prolonged-release tablets - Summary of Product Characteristics (SmPC) - (emc) 2. BNF https://bnf.nice.org.uk/drugs/melatonin/ accessed 22/10/24. 3. PrescQIPP bulletin 318, January 2023 318. Melatonin 2.0 accessed 22/10/24. 4. https://www.sps.nhs.uk/articles/treating-insomnia-during-breastfeeding/ accessed 22/10/24.