

## **NHS South West Essex Shared Care Guideline**

### **Melatonin for the treatment of sleep disorders in children and adolescents (unlicensed use)**

#### **Introduction**

##### **Indication**

Melatonin is used to improve the onset and duration of sleep in infants, children and adolescents with neurological and/or behavioural problems who have severe sleep disturbance. It can also be used to improve onset and duration of sleep in children and adolescents with congenital or acquired neurological/neurodevelopmental problems including conditions such as learning difficulties, autistic spectrum disorders, ADHD, cerebral palsy, visual impairment, epilepsy and neurodegenerative disorders.

The treatment of choice for sleep disturbance is behavioural. Melatonin should be used in conjunction with behavioural management techniques or if sleep hygiene/behavioural treatment has been unsuccessful.

##### **Pharmacology**

Sleep disturbance in children and adolescents is common, especially in those with neurological and/or behavioural disorders. This sleep disturbance may include delayed onset of sleep, frequent waking, early morning waking or day-night reversal of sleep pattern. Melatonin is a hormone secreted by the pineal gland which has an important role in the regulation of circadian rhythm. Administration of synthetic melatonin promotes the onset of sleep and has been used for the management of sleep difficulties in adults and children. Modified release melatonin (Circadin<sup>®</sup>) is the preferred first line melatonin preparation for use, where appropriate.

#### **Dosage and administration**

##### **Problems with sleep initiation**

Standard release melatonin is used in children and adolescents who have problems with sleep initiation. The starting dose is usually 2mg to 3mg given 30 to 60 minutes before bedtime. If there is no response or insufficient response after a minimum of seven days therapy, the dose can be increased by 1mg or 2mg increments. The dose can be increased up to a maximum dose of 10mg. There are no licensed immediate release melatonin preparations available. Immediate release preparations are available in the UK from specials manufacturers. TEMAG Pharma Limited produce a range of cost effective immediate release melatonin products, including capsules and oral suspension.

### **Problems with sleep maintenance/fragmental sleep and/or early morning awakening**

If there is a significant problem with sleep maintenance/fragmental sleep and/or early morning awakening then modified release melatonin, such as Circadin<sup>®</sup>, may be used in the first instance.

In some children a combination of standard release melatonin and modified release melatonin may be required, up to a maximum total dose of 10mg.

### **Reviewing treatment**

If treatment is successful, a trial reduction in dose should be attempted after 6 months as some patients will have settled into a regular sleep pattern and may not need to continue at the same dose or may even be able to maintain sleep with no medication. If sleep patterns are maintained, dosage can be reduced by 2mg every 4 to 6 weeks. If difficulties recur the original dose should be reinstated immediately but a further trial reduction should be attempted 6 to 12 months later. The specialist will initiate this at a clinic review if considered appropriate. Some children/adolescents with a development or neurological problem may require long term treatment.

### **Products and strengths available**

#### **Licensed modified release melatonin**

- A licensed melatonin 2mg modified release tablet (Circadin<sup>®</sup>) is available. This is only licensed in adults aged 55 years or over as short term treatment of primary insomnia, and therefore would be an unlicensed use in children and adolescents.
- Modified release melatonin (Circadin<sup>®</sup>) is the preferred first line melatonin preparation for use, where appropriate.

#### **Standard release melatonin (unlicensed)**

- A range of strengths and formulations of unlicensed melatonin are available.
- The unlicensed brand Melajet produced by the manufacturer TEMAG Pharma Limited represents a cost effective melatonin product.

<b>TEMAG Pharma Limited melatonin product</b>	<b>Pack size</b>
Melajet melatonin 1mg capsules	60
Melajet melatonin 2mg capsules	60
Melajet melatonin 3mg capsules	60
Melajet melatonin 5mg capsules	60
Melajet melatonin 2.5mg/5ml oral suspension	150ml
Melajet melatonin 5mg/5ml oral suspension	150ml

- The brand and manufacturer of melatonin should be specified on the prescription, to help to maintain the patient on the same brand, due to variability in clinical effect of unlicensed formulations (BNF for children recommendation).
- Melatonin 5mg/5ml oral solution and 5mg/5ml oral suspension are listed as part of the Drug Tariff unlicensed specials list. Therefore, there is a standard reimbursement price for these products for which payment will be calculated for the dispensing of that drug, regardless of how the product was sourced by the community pharmacy. It is more cost effective for melatonin 5mg/5ml to be prescribed as oral solution, based on the Drug Tariff reimbursement price.

### **Responsibilities of the specialist initiating treatment**

- To assess the suitability of the patient for treatment and confirm that a trial of behavioural management has been attempted and failed. A sleep diary<sup>1</sup> may be useful in determining the nature and severity of the sleep disorder prior to commencing treatment.
- To discuss the benefits and side effects of treatment with the patient/carer and the need for long term monitoring before initiating treatment.
- Explain the unlicensed nature of melatonin, and obtain consent to treatment from the patient/parents/carer as applicable.
- To provide patient/carer with a written factsheet. Parent information leaflet is available for use.
- To initiate treatment and adjust according to patient response.
- When the patient is near completing a satisfactory initiation period, the specialist to write to the GP to request that they take over prescribing and participate in the shared care arrangements. To continue prescribing, in the event that a GP is not willing to participate in the shared care arrangement.
- To review the patient in clinic twice per year.
- To perform drug monitoring as detailed below.
- To adjust the dose and formulation of melatonin as required and communicate this information to the GP.
- To stop medication when indicated.
- To monitor the patient for adverse events and report to the GP and where appropriate the MHRA (Yellow card reporting scheme).

### **Baseline Assessment**

- Height and weight
- Sleep diary<sup>1</sup> (see below)

### **Monitoring**

- Height and weight every 6 months.
- Pubertal maturation progress.
- Seizure frequency in epileptic patients.

- Have a telephone consultation with the parent every month until optimum dose established. Following this they will be seen twice per year for review.
- Consider with the family the need for a trial reduction of melatonin as described above.

### **Responsibilities of the GP/primary care**

- If do not agree to participate in shared care, discuss with specialist on receipt of shared care request.
- To prescribe melatonin at the dose and formulation recommended by the specialist.
- To consider the most cost effective formulation and preparation of melatonin to prescribe.
- To make adjustments to the dose of melatonin within the agreed dosage regime if these are indicated and communicate these to the specialist in writing.
- To liaise with the specialist regarding any problems with the treatment.
- To identify adverse effects if the patient presents with any signs and liaise with the specialist where necessary. To report suspected adverse effects to the specialist and where appropriate the MHRA (Yellow card reporting scheme).

### **Responsibilities of the parent/carer**

- To report any suspected adverse effects to the specialist or GP whilst taking medication.
- To share any concerns in relation to treatment with melatonin.
- To report to the specialist or GP if they do not have a clear understanding of the treatment.
- Attend appointments for review as agreed with specialist or GP.
- To keep a sleep diary to assess the effectiveness of therapy if requested.

<sup>1</sup>**Sleep diary**-A sleep diary can be useful to help parents find out what triggers poor sleep behaviour and what seems to help. A sleep diary might contain:

- The time the child went to sleep and the number of times awake during the night.
- The number and length of naps during the day to see if cutting down naps and keeping the child awake for longer periods during the day helps.
- The process of preparing the child for bed to identify whether changes to bedtime routine work well.
- Medication and time given as giving medication at different times of the day might help.

## **Adverse drug reactions, cautions and contraindications, and drug interactions**

### **Adverse drug reactions**

- Melatonin is generally well tolerated. The available literature suggests that melatonin is safe. Less common side effects (as detailed in BNF for children) include abdominal pain, dyspepsia, dry mouth, mouth ulceration, weight gain, hypertension, chest pain, malaise, dizziness, restlessness, nervousness, irritability, anxiety, migraine, proteinuria, glycosuria, pruritus, rash, dry skin (please refer to BNF for children for further side effects).
- It has been suggested that melatonin may affect the reproductive system by inhibiting the hypothalamic-pituitary-gonadal axis. It would be advisable to monitor growth and sexual development, especially with long term melatonin use.
- Young people up to the age of 20 years produce melatonin endogenously in high levels and levels are inversely related to gonadal development. In the clinical trials, there is no reported association between melatonin and delayed onset of puberty.
- The adverse effects of modified release melatonin are not expected to differ to those from the standard release melatonin preparation.

### **Contraindications, special warnings and precautions for use**

- Hypersensitivity to the active substance or any of the excipients.
- The manufacturers of Circadin<sup>®</sup> state that it should not be taken in patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption. It is also not recommended for use in patients with auto-immune diseases.
- Caution in renal or hepatic disorders.

### **Cautions: Use in patients with epilepsy**

There have been conflicting reports on the effect of melatonin on seizure activity. Some reports suggest melatonin improves seizure control whilst others indicate that it may worsen seizure control. It is advisable to give the antiepileptic an hour before melatonin as absorption can be reduced by the antiepileptic. When using melatonin in patients with epilepsy, seizure frequency should be closely monitored.

### **Drug Interactions (detailed in Circadin<sup>®</sup> 2mg prolonged release tablets Summary of Product Characteristics)**

- Caution should be exercised in patients on fluvoxamine, which increases melatonin levels. The combination should be avoided.
- Caution should be exercised in patients on 5- or 8-methoxypsoralen (5 and 8-MOP), which increases melatonin levels by inhibiting its metabolism.
- Caution should be exercised in patients on cimetidine, which increases plasma melatonin levels, by inhibiting its metabolism.

- Caution should be exercised in patients on oestrogens (e.g. contraceptive therapy), which increase melatonin levels by inhibiting its metabolism.
- CYP1A2 inhibitors such as quinolones may give rise to increased melatonin exposure.
- CYP1A2 inducers such as carbamazepine and rifampicin may give rise to reduced plasma concentrations of melatonin.
- Circadin<sup>®</sup> may enhance the sedative properties of benzodiazepines and non-benzodiazepine hypnotics, such as zaleplon, zolpidem and zopiclone. In a clinical trial, there was clear evidence for a transitory pharmacodynamic interaction between Circadin<sup>®</sup> and zolpidem one hour following co-dosing. Concomitant administration resulted in increased impairment of attention, memory and co-ordination compared to zolpidem alone.

Please refer to BNF Appendix 1 for further information regarding drug interactions.

### **Patient Information**

Medicines for Children have also produced a PIL and is available via <http://www.medicinesforchildren.org.uk/search-for-a-leaflet/melatonin-for-sleep-disorders/>

### **References/Acknowledgements**

- Circadin 2mg prolonged release tablets, Summary of Product Characteristics, <http://www.medicines.org.uk/EMC/medicine/25643/SPC/Circadin/>, accessed 20/11/2012
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- Guidelines on Melatonin-Alderhey Children's Hospital
- Melatonin-for the treatment of sleep disorders in disabled children and CAMHS patients-Derbyshire NHS Trust
- Professor G Stores – Oxford, archives, 2003
- Melatonin Information for families- Great Ormond Street Hospital
- Melatonin and sleep in children with neurodevelopmental disabilities and sleep disorders: Current Paediatrics (2006)
- Treatment of Sleep-Wake Cycle Disorders in Children, NHS Lothian, Dec 2006
- Sleep Disorders in Children, BMJ
- Melatonin in Paediatric Sleep Disorders, London New Drugs Group, January 2008
- Information for Community Pharmacists on Melatonin
- Information for GPs, Developmental Medicine Child Neurology 2004
- BNF for children 2012-2013, published by BMJ Group

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