

**North of Tyne Area Prescribing Committee
Shared Care Group**

MELATONIN – Information for Primary Care

Background

Melatonin is a hormone secreted by the pineal gland. It is normally secreted at night and its main function is the regulation of circadian rhythm and sleep, playing an important role in setting the correct timing of sleep-wake cycles.

The administration of exogenous melatonin has a rapid, transient, mild sleep inducing effect and it lowers alertness, body temperature and performance for about 3 to 4 hours after the administration of low doses (of immediate release formulations).

Melatonin has been used in the UK as an unlicensed medicine for several years on the advice of hospital specialists, for limited use in the treatment of a variety of sleep disorders. A licensed modified release product is also available. The North of Tyne Area Prescribing Committee has approved the use of melatonin for the following indications:

Approved Indications

Melatonin can be used to facilitate the induction of sleep, and increase the duration of sleep on the advice of an appropriate secondary care specialist, in the following situations:

- 1) Visually impaired or blind people with disturbed sleep wake cycles.
- 2) Delayed sleep phase syndrome and other circadian rhythm disorders.
- 3) Children with neurological or behavioural disorders including:
 - Attention deficit hyperactivity disorder (ADHD).*
 - Chronic sleep onset insomnia.*
 - Neurodevelopmental disabilities (e.g. involving delayed brain maturation, sensory dysfunction - especially visual and dysfunction of sleep centres).*
- 4) Treatment of children and young adults with chronic fatigue syndrome / myalgic encephalomyelitis who have sleep difficulties (as recommended in NICE clinical guideline no. 53).*
- 5) Prior to examinations such as a sleep encephalogram (EEG) in children and sedation prior to scans in paediatric oncology.
- 6) Patients with REM sleep behaviour disorder (RBD) - e.g. associated with degenerative conditions such as Parkinson's disease or dementia, as a second line treatment to clonazepam.
- 7) To improve nocturnal sleep in critically ill patients (to aid weaning from mechanical ventilation).

*Note that for indications 3 and 4 in children and young people melatonin is classified as an 'amber' drug by the NoT APC therefore subject to formal shared care guidance. This is available at:

<http://www.northofityneapc.nhs.uk/files/2013/03/Melatonin-in-children-and-young-people-March-2013.pdf>

The use of melatonin for the above indications is unlicensed. It is usually used as a second or third line therapy - where sleep problems are adversely affecting quality of life in patients where other methods of management, including non pharmacological treatments, have failed to work, are not tolerated or are impracticable.

Dose

As advised by specialist - typically:

Children and Adults:

Initially 2 to 3mg at night, increased if necessary after 1-2 weeks to 4-6mg at night.

Usual maximum dose is 10mg at night.

For circadian rhythm disorders the medication should be given at a fixed time as advised by the specialist

Immediate release product – the dose should be given 30 to 60 minutes before bedtime

Modified release melatonin product should be given 1-2 hours before bedtime and after food

Treatment should be stopped in those who fail to respond to the maximum dose.

In those requiring long-term treatment, the specialist may advise attempting a reduction in dose after several months in patients who have settled into a regular sleep pattern.

Monitoring

Treatment with melatonin should be initiated and supervised by a specialist and if used long-term, the need for continuing therapy should be reviewed regularly. Treatment should be stopped in patients who do not continue to benefit from its use. Monitoring, particularly with regard to growth and pubertal/sexual development, is advised in children during long term administration, especially in those receiving melatonin for periods of a year or more.

Cautions

- 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 autoimmune diseases or taking immunosuppressants.
- Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take Circadin brand melatonin. (contains lactose).
- Patients with hepatic impairment.
- Melatonin may worsen restless legs syndrome.

Also see drug interactions.

Contra-indications

Children under 1 year of age, pregnancy, breastfeeding, hypersensitivity to melatonin or any excipients. Not recommended for use in individuals with autoimmune diseases or hepatic impairment.

Drug Interactions

Fluvoxamine	Avoid use with melatonin as melatonin plasma concentrations are markedly increased (metabolism inhibited).
5 and 8-methoxypsoralen Cimetidine Oestrogens Ciprofloxacin and other quinolones	Use with caution with melatonin, increased melatonin plasma concentration.
Alcohol	Avoid – reduces effectiveness of melatonin.
Cigarette smoking	May reduce melatonin concentrations.
Other hypnotics and CNS depressants	Melatonin may enhance the sedative properties of other drugs acting on the CNS e.g. benzodiazepines.

Adverse Effects

Melatonin is generally well tolerated and adverse reactions reported are at similar levels to those reported with placebo.

Tiredness, headaches, dizziness, pharyngitis, back pain, asthenia and irritability have been reported following its use. Other rare side effects include restlessness, confusion, increased heart rate, itching and nausea.

High doses can reduce body temperature.

Discontinuation does not appear to be associated with withdrawal effects.

Formulations and Availability

Melatonin is freely available to purchase in some countries as a 'nutritional supplement' but in the UK access is restricted to supply by prescription.

Since the launch of the licensed product, Circadin - melatonin 2mg modified release (m/r) tablets - in June 2008, the MHRA has restricted the importation of unlicensed formulations of melatonin. However, unlicensed formulations made in the UK remain readily available from UK licensed 'Special Order' manufacturers.

<p>Preferred Product 2mg modified release tablets* (Available as the licensed product Circadin)</p>	<p>This is the preferred formulation for use where it is clinically appropriate</p>
<p>Alternatives 1mg, 2mg*, 2.5mg*, 3mg, 5mg* and 10mg capsules or tablets 2mg and 3mg orodispersible tablets 1mg/ml oral solution*</p>	<p>Available as unlicensed medicines. See note 2 below.</p>
<p>Notes</p> <ol style="list-style-type: none"> 1. Only the products marked * are included in the North of Tyne Formulary 2. Guidance from the MHRA states that those supplying melatonin (as with other unlicensed medicines) must keep the following records for 5 years: <ul style="list-style-type: none"> • The source of the product. • The person to whom and the date on which the product was sold or supplied. • The quantity of each sale or supply. • The batch number of the product. • Details of any adverse reactions to the product sold or supplied of which he is aware. <p>These records must be made available for inspection by the licensing authority, and serious adverse drug reactions must be reported to the MHRA (via the yellow card scheme).</p>	

To ensure that the Penn or Special Products formulation is supplied, prescribers will need to specify (e.g., Penn) on every prescription.

Availability

Melatonin 2mg modified release tablets (licensed)

These are readily available to pharmacies through pharmaceutical wholesalers.

Melatonin Unlicensed Formulations

These are available from a number of 'Special Order' manufacturers/distributors including:

Special Products Ltd⁺		Penn Specials Manufacturing	
<i>Unit 16, Trade City, Avro Way,</i>	2mg capsules	<i>Tredegar, Gwent, NP22 3AA</i>	1mg, 2mg, 2.5mg, 3mg, 5mg & 10mg capsules
<i>Brooklands Business Park, Weybridge, Surrey, KT13 0YF</i>	3mg capsules	<i>Tel: 01495 711222</i>	2mg & 3mg orodispersible tablets
<i>Tel: 01932 690325</i>	1mg in 1ml oral solution	<i>Fax: 01495 713613</i>	
<i>Fax: 01932 341091</i>		<i>Email: sales@pennpharm.com</i>	
<i>Email: info@specialproducts.biz</i>			
Pharma Nord (UK) Ltd.		The Specials Laboratory Ltd	
<i>Telford Court Morpeth Northumberland NE61 2DB</i>	3mg tablets – available as Bio-Melatonin*	<i>Unit 1 Regents Drive Low Prudhoe Industrial Estate Northumberland NE42 6PX</i>	The specials laboratory can supply a wide range of melatonin formulations
<i>Tel: 01670 519989</i>		<i>Tel: 0800 028 4925</i>	
<i>Fax: 01670 534903</i>		<i>Fax: 0800 083 4222</i>	
<i>E-Mail: rdixon@pharmanord.com</i>		<i>Email: orders@specialslab.co.uk</i>	
At the present time the 3mg tablets from PharmaNord and the products from the Specials Products Ltd are available at a lower cost than products from other sources.			
* Melatonin products supplied by Special Products Ltd are currently less expensive than those supplied from most other sources.			
* For the initial supply PharmaNord requires a letter from a doctor stating that Pharma Nord Bio-Melatonin 3mg tablets is required as an unlicensed medicine, because the licensed product does not meet the clinical need of the patient for a stated reason. Once this has been received further supplies can be made against an order signed by a pharmacist.			

Costs

	NHS cost of treatment ^a	
	7 days	28 days
Licensed Melatonin 2mg m.r. tablets (Circadin) 2mg at night	£3.59	£14.26 ^b
Unlicensed Melatonin Products		
<i>Melatonin capsules^c</i>		
2mg at night	£4.03 - £11.17	£16.12 - £44.68
2.5mg at night	£4.03 - £9.38	£16.12 - £37.52
5mg at night	£4.03 - £10.98	£16.12 - £43.92
Melatonin 1mg/ml oral solution		
3mg at night	£14.87	£59.48
a) The above costs are based on prices from 3 suppliers and do not include any delivery charges, or VAT. Costs from others sources may differ.		
b) Licensed dose 2mg at night for up to 3 weeks.		
c) The contents of the capsules can be emptied and administered in a drink/soft food as an alternative to using the oral solution.		