



Greater Manchester Interface Prescribing Group Shared Care Guideline

Shared Care Guideline for <i>Melatonin Circadin</i>		Reference Number Version 1
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Please complete all sections

1. Licensed Indications

Unlicensed Indication: the treatment of sleep disorders in children and adolescents.

2. Therapeutic use & background

Sleep disturbances in children with neurological or behavioural disorders are very common. There are multiple factors for this that are frequently interrelated and which include delayed brain maturation, malfunction of sensory organs (particularly vision) and abnormalities or malformations of the sleep centres.

Melatonin is increasingly being considered for the treatment of insomnia in children and adolescents with neurodevelopmental or psychiatric disorders such as autistic spectrum disorder and attention deficit hyperactivity disorder (ADHD).

The types of sleep disruption experienced include delayed onset, frequent waking, early morning wakening and reversal of the day-night sleep pattern. Such children have a variable response to behavioural therapies. The use of traditional hypnotics or sedative drugs can cause adverse reactions and lead to tolerance and dependence. For these reasons other treatments are desirable.

Melatonin is an endogenous hormone produced by the pineal gland in the brain. It is important in the regulation of the circadian rhythms in humans and animals and a number of studies have shown that exogenous melatonin has beneficial effects on the sleep patterns of these kinds of children.

3. Contraindications (please note this does not replace the SPC or BNF and should be read in conjunction with it).

Autoimmune disease
Hepatic Impairment: manufacturer advises avoid
Hypersensitivity to the active substance or to any of the excipients.
Melatonin may cause drowsiness. Therefore the product should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety.
Renal Impairment: no information available – manufacturer advises caution

4. Prescribing in pregnancy and lactation

This drug cannot be prescribed in the pregnant/breastfeeding patient. Under these circumstances prescribing should be the responsibility of *the specialist*

5. Dosage regimen for continuing care

Route of administration *Oral*

Preparations available (include in this section any necessary information relating to availability of special preparations for children or those with swallowing difficulties)

Melatonin 2mg tablets **Circadin®** brand only to be prescribed in primary care. Within Pennine Care and Pennine Acute melatonin liquid may be prescribed and initiated on an *exceptional basis only*. Liquid melatonin preparations are extremely high cost items to both the Trust and PCT and should only be used where absolutely necessary.

For swallowing difficulties see Administration section below.

Insert dose to be prescribed including units, frequency and duration of treatment.

The recommended dose is initially 2mg once daily, increased if necessary after 1-2 weeks to 4-6mg. Max 10mg.

The dose should be taken 1-2 hours before bedtime.

Administration

Tablets should be swallowed whole with a drink. They can be taken with or without food.

For patients with swallowing difficulties, Circadin® 2mg tablets, can be crushed but do not dissolve well in water.

For children with difficulties swallowing, the tablet can be crushed to a fine powder and mixed with water or jam. Use a small amount of food to ensure the full dose is taken.

Once crushed, the tablet will **not** retain its slow release characteristics. Therefore the prescription should state that the medication is to be crushed prior to administration.

Where Circadin® 2mg tablets need to be administered via a gastrostomy tube they should be crushed (as above) and flushed through the tube with plenty water.

The manufacturers of Circadin® have stated that halving the tablets is not likely to affect the prolonged-release matrix; however, the tablets are not scored, and so this would need to be done carefully to ensure the tablet is not crushed in the process.

Crushing or halving the tablets will render the product unlicensed and the manufacturers do not have any stability data to support this method of administration.

Is titration required Yes / No (please circle as appropriate)

Titrate dosage up by *2mg every 1-2 weeks* according to response.

Maintenance dosage up to a maximum 10mg daily

Adjunctive treatment regime

NA

Usual response time

If there has been no beneficial response within 7-14 days, the dose can be increased in 2mg steps every 7-14 days, up to a maximum of 10mg daily

There is no evidence to suggest higher doses provide additional benefits and where patients fail to respond to treatment at the maximum doses stated above, treatment should be discontinued. This can be done abruptly

Treatment Breaks

Where patients benefit from treatment there should be follow up every 3-6 months to assess continued need. These can take the form of treatment holidays, where the melatonin is gradually withdrawn over a period of 3-4 weeks and change in sleeping pattern observed. For some children however withdrawal is not successful and treatment may need re-instating for a further period.

It is suggested that at least three to six months of an improved sleep pattern should elapse before withdrawal takes place. The specialist will organise this withdrawal and inform the GP to hold prescriptions for that time period, and where necessary to re-start.

NB. All dose adjustments will be the responsibility of the initiating specialist care unless directions have been specified in the medical letter to the GP.

6. Drug Interactions

For a comprehensive list consult the BNF or Summary of Product Characteristics

The following drugs interact with melatonin:

Fluvoxamine
5- or 8-methoxypsoralen
Cimetidine
Cigarette smoking
Oestrogens (e.g. contraceptive or hormone replacement therapy)
Quinolones
Carbamazepine
Rifampicin
Alcohol

There is a large amount of data in the literature regarding the effect of adrenergic agonists/antagonists, opiate agonists/antagonists, antidepressant medicinal products, prostaglandin inhibitors, benzodiazepines, tryptophan and alcohol, on endogenous melatonin secretion. Whether or not these active substances interfere with the dynamic or kinetic effects of Circadin® or vice versa has not been studied.

Circadin® 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® and zolpidem one hour following co-dosing. Concomitant administration resulted in increased impairment of attention, memory and co-ordination compared to zolpidem alone.

Circadin® has been co-administered in studies with thioridazine and imipramine, active substances which affect the central nervous system. No clinically significant pharmacokinetic interactions were found in each case. However, Circadin® co-administration resulted in increased feelings of tranquillity and difficulty in performing tasks compared to imipramine alone, and increased feelings of “muzzy-headedness” compared to thioridazine alone.

7. Adverse drug reactions

Specialist to detail below the action to be taken upon occurrence of a particular adverse event as appropriate. Most serious toxicity is seen with long-term use and may therefore present first to GPs.

For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event uncertain, consult Summary of Product Characteristics or BNF

Adverse event System – symptom/sign	Action to be taken Include whether drug should be stopped prior to contacting secondary care specialist	By whom
<i>New onset Seizures</i>	<i>Refer to the specialist, stop medication</i>	<i>GP</i>
<i>Abdominal pain, dyspepsia</i>	<i>Refer to the specialist, keep on medication</i>	<i>GP</i>
<i>Cardiac symptoms</i>	<i>Refer to the specialist, stop medication</i>	<i>GP</i>
<i>Aggression/Agitation</i>	<i>Refer to the specialist, keep on medication</i>	<i>GP</i>
<i>Restlessness/nervousness</i>	<i>Refer to the specialist, keep on medication</i>	<i>GP</i>

The patient should be advised to report any of the following signs or symptoms to their GP without delay:

New onset seizures, cardiac symptoms, agitation/aggression

Other important co morbidities (e.g. Chickenpox exposure). Include advice on management and prevention and who will be responsible for this in each case:
N/A

Any adverse reaction to a black triangle drug or serious reaction to an established drug should be reported to the MHRA via the “Yellow Card” scheme.

8. Baseline investigations

List of investigations / monitoring undertaken by secondary care
Sleep Diary

9. Pharmaceutical aspects

*e.g. special storage requirements, washout periods Or where there are “no special considerations”
no special considerations*

10. Secondary care contact information

If stopping medication or needing advice please contact:

Dr *[insert text here]*_____

Contact number: *[insert text here]*_____

Hospital: *[insert text here]*_____

11. Criteria for shared care

Prescribing responsibility will only be transferred when:

- The GP has agreed in writing in each individual case that shared care is appropriate.
- Treatment is for a specified indication and duration.
- Treatment has been initiated and established by the secondary care specialist
- The patient’s initial reaction to and progress on the drug is satisfactory.
- The patient’s general physical, mental and social circumstances are such that he/she would benefit from shared care arrangements

12. Specialist responsibilities

- Make any necessary diagnosis and communicate these to the GP and any other professionals involved in the patient’s care including what non-pharmacological strategies have been performed.
- Discuss treatment options with the patient, their parent(s)/ carer(s), to include explanation of the off licence nature of melatonin, the benefits and side effects, obtaining appropriate consent to treatment and to share care with the GP.
- Request the GP to take over prescribing in a clear letter, the letter should include full clinical details and document that the off licence nature of melatonin has been discussed and consent obtained.
- Initiation and titration of melatonin to a suitable dose.
- Follow up every 3-6 months to ensure continuing benefit of melatonin
- Ensure that the appropriate monitoring is undertaken.
- When appropriate, undertake periodic treatment withdrawals, or advise the GP in writing how and when to undertake them
- If a treatment withdrawal period is required the specialist will coordinate with the GP to stop prescribing for this time period
- Regular communication of clinical progress, changes, recommendations, outcomes or other important information to the GP
- Provide advice to the GP if they have clinical queries relating to the

condition or use of melatonin

- Report any adverse events to the MHRA
- To take responsibility for stopping the melatonin or to agree aftercare when the patient reaches 18 years of age

13.GP Responsibilities

- Reply to the request for shared care within 14 days of receiving the document.
- Continued prescribing of melatonin under guidance of the Specialist.
- Carry out further dose titration according to the schedule suggested, or discontinue the medication, when necessary or requested.
- Ask patient/parent/carer about effectiveness and side effects.
- Ensure no drug interactions with any concomitant medicines
- Communicate any problems to the consultant looking after the patient.
- If the specialist requests a treatment withdrawal period, the GP would need to put a hold on the prescriptions until they receive confirmation that they are to re-start
- Report any suspected adverse drug reactions to the Specialist who initiated therapy under the shared care agreement, all adverse events should be reported even if causal relationship is not known or if the adverse event is already known about. Report adverse events to the MHRA
- Only ask the consultant to take back the prescribing should unmanageable problems arise and allow an adequate notice period (4 weeks is the suggested minimum)

14.Patient and Parent/Carer Responsibilities

- Discuss potential benefits and side effects of treatment with the specialist and GP, to identify whether they have a clear picture of these from the specialist and to raise any outstanding queries.
- Share any concerns they have in relation to treatment with their drug(s)
- Report any adverse effects to their specialist or GP whilst taking drug(s)
- Report to the specialist or GP if they do not have a clear understanding of their treatment
- Participate in the monitoring of therapy and the assessment of outcomes, to assist health professionals to provide safe, appropriate treatment
- Attend GP and hospital appointments

15. Additional Responsibilities	List any special considerations	Action required	By whom	Date
	<i>[insert]</i>	<i>[insert]</i>	<i>[insert]</i>	<i>[insert]</i>
	<i>[insert]</i>	<i>[insert]</i>	<i>[insert]</i>	<i>[insert]</i>

16. Supporting documentation

The SCG must be accompanied by a patient information leaflet.

17. Patient monitoring booklet

N/A

18. Shared care agreement form

Attached below

Shared Care Agreement Form

Specialist request

***IMPORTANT: ACTION NEEDED**

Dear Dr *[insert Doctors name here]*

Patient name: *[insert Patients name here]*

Date of birth: *[insert date of birth]*

Diagnosis: *[insert diagnosis here]*

This patient is suitable for treatment with *[insert drug name]* for the treatment of *[insert indication]*

The off licence nature of melatonin has been discussed with the patient and the parents/responsible carer(s) and they have consented to its use.

This drug has been accepted for Shared Care according to the enclosed protocol (as agreed by Trust / LHB / AWMMSG). I am therefore requesting your agreement to share the care of this patient.

Treatment was started on *[insert date started]* *[insert dose]*.

If you are in agreement, please undertake treatment from *[insert date]*

NB: date must be at least 1 month from initiation of treatment.

Baseline tests: *[insert information]*

Next review with this department: *[insert date]*

You will be sent a written summary within 14 days. The medical staff of the department are available at all times to give you advice. The patient will not be discharged from out-patient follow-up while taking *[insert text here]*.

Please use the reply slip overleaf and return it as soon as possible.

Thank you.

Yours

[insert Specialist name]

Contact number: *[insert text here]* _____

Shared Care Agreement Form

GP Response

Dear Dr *[insert Doctors name]*

Patient *[insert Patients name]*

Identifier *[insert patient date of birth/address]*

I have received your request for shared care of this patient who has been advised to start *[insert text here]*

- A I am willing to undertake shared care for this patient as set out in the protocol
- B I wish to discuss this request with you
- C I am unable to undertake shared care of this patient.

GP signature

Date

GP address/practice stamp