SHARED CARE PRESCRIBING GUIDELINE MELATONIN

DOCUMENT DETAILS

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Relevant external law, regulation, standards	
Comments on this document to:	Clinical Governance Pharmacist c/o Pharmacy Department, Guy's Hospital

CHANGE HISTORY

Date	Change details	Approved by
June 2011	Changes made based on feedback from Lambeth PCT	

Melatonin

Off- label use for REM sleep behaviour disorder & Circadian rhythm sleep disorders (delayed sleep phase disorder, irregular sleep wake rhythm and free running disorder)

NOTES to the GP

The information in the shared care guideline has been developed in consultation with Primary Care and it has been agreed that it is suitable for shared care.
This document should provide sufficient information to enable you to make an informed decision regarding the clinical and legal responsibility for prescribing this drug.

The questions below will help you confirm this:

- Is the patient's condition predictable or stable?
- Do you have the relevant knowl edge, skills and access to equipment to allow you to monitor treatment as indicated in this shared care prescribing guideline?
- Have you been provided with relevant clinical details including monitoring data?

If you can answer YES to all these questions (after reading this shared care guideline), then it is appropriate for you to accept prescribing responsibility.
If the answer is NO to any of these questions you should contact the requesting consultant or your local PCT medicines management team. It would not normally be expected that shared care prescribing would be declined on the basis of cost.

Prescribing should follow requirements in the South East London Interface Prescribing Policy
The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use. The patient's best interests are always paramount

Date shared care guideline prepared: July 2008 then updated Aug 2010 **Approved by:** Medicines Management Committee. Lambeth & Southwark PCT 31 Oct 2011 **Approved by DTC:** GSTFT 10 Nov 2011 **Review date:** Nov 2013	**Prepared by:** Dr Chris Kosky (Consultant Physician, Sleep Centre) Gráinne d'Ancona (Principal Pharmacist, Acute Medicine)

REQUEST FOR SHARED CARE

Consultant Name:	**Patient name:**
Consultant signature:	**Hospital Number:** **NHS Number:**
Date completed:	**D.O.B**
GP Name	**Diagnosis/Indication**

ACTION

HOSPITAL:

- Email/Fax completed shared care guideline to GP for attention and action
- F**ax details for GPs** can be found **www.nhs.uk/**
- Original to be filed in Patient's clinical record

GP PRACTICE:

- Please consider request within 2 weeks
- If named GP is not available over the next week pass request to a GP colleague.
- **If agree** to request initiate prescribing as detailed in shared care guideline. Confirmation to the requesting consultant is not required, it will be assumed after 2 weeks.
- **If do not agree** to request contact consultant or local PCT medicines management team within 2 weeks of receipt to discuss. If after discussion it is agreed not to undertake shared care for this patient, both the consultant and the local PCT Medicines Management team should be informed.
- Once decision reached file copy in patient's notes.

Attach patient addressograph

Melatonin

This medicine is monitored intensively by the CHM and MHRA

1. CIRCUMSTANCES WHEN SHARED CARE IS APPROPRIATE

- Prescribing responsibility will only be transferred when the consultant and the GP are in agreement that the patient's condition is stable or predictable.
- The hospital will provide the patient with a supply of therapy until the patient is stable.

2. AREAS OF RESPONSIBILITY

Consultant	GP
▪ Establish or confirm diagnosis and assess patient suitability for treatment ▪ Baseline monitoring There are no baseline monitoring requirements for melatonin ▪ Discuss treatment with patient and ensure they have a clear understanding of it. ▪ Melatonin can cause drowsiness. Drowsiness may effect performance of skilled tasks such as driving. Patients should not drive if they feel sleepy. Fax a signed shared care guideline with patient details completed to GP for consideration of shared care request ▪ Initiate treatment and provide a minimum of 2 weeks supply to the patient. ▪ Prescribe and monitor treatment according to local guideline or formulary until patient's condition is stable or predictable *After agreement to shared care* ▪ Inform GP when patient is stable and responding the therapy ▪ Inform GP of abnormal monitoring results and any changes in therapy ▪ Evaluate adverse events reported by GP or patient ▪ Carry out ongoing monitoring and follow up accordingly to shared care guidelines including continued need for therapy.	▪ Consider shared care proposal within 2 weeks of receipt ▪ If agreement to shared care take over prescribing responsibility. Confirmation to the requesting consultant is not required, it will be assumed after 2 weeks. ▪ If do not agree to shared care discuss with requesting consultant or local PCT medicines management team within 2 weeks of receipt of shared care request *After agreement to shared care* ▪ Prescribe dose as recommended once the patient's condition is stable or predictable ▪ Monitor general health of patient and check adverse effects as appropriate ▪ Inform specialist consultant of suspected adverse effects and also report via yellow card scheme if necessary ▪ Stop treatment on advice of specialist or immediately if urgent need arises ▪ Check compatibility interactions when prescribing new or stopping existing medication ▪ Carry out monitoring and follow up according to shared care guideline ▪ Discuss any abnormal results with specialist consultant and agree any action required ▪ Only ask specialist to take back prescribing should unmanageable problems arise. Allow an adequate notice period.

3. PATIENTS RESPONSIBILITIES (add specific additional responsibilities where applicable)

- Take medicines as agreed
- Report any adverse effects to GP or hospital doctor
- Do not share medicines

4. COMMUNICATION AND SUPPORT

Hospital contacts:

SLEEP DISORDERS CENTRE
St. Thomas's Hospital, Lambeth Palace Road, SE1 7EH
Tel: 0207 188 8937
Fax: 0207 188 6114

Specialist Consultant physicians :
Prof Adrian Williams:
Adrian.Williams@gstt.nhs.uk
Dr Chris Kosky:
Chris.Kosky@gstt.nhs.uk
Dr Rexford Muza:
Rexford.Muza@gstt.nhs.uk
Dr Guy Leschziner;
Guy.Leschziner@gstt.nhs.uk
Dr Joerg Steier
Joerg.Steier@gstt.nhs.uk

Attach patient addressograph

Melatonin

5. CLINICAL INFORMATION[1]

Indication(s):	Off label use: REM sleep behaviour disorder & Circadian rhythm sleep disorders (delayed sleep phase disorder, irregular sleep wake rhythm and free running disorder)
Place in Therapy:	REM sleep behaviour disorder is characterised by the loss of normal paralysis during REM sleep with dream enactment. It commonly leads to injury. Medication is used to prevent injury. Melatonin is used as first line therapy because it has minimal side effect. Clonazepam is the alternative first line option. Circadian rhythm sleep disorders include delayed sleep phase syndrome and free running disorder. Delayed sleep phase syndrome is characterised by a stable sleep schedule that is substantially later than the conventional or desired sleep time. Patients have sleep onset insomnia and difficulty arising to conform to a conventional work schedule. Free running disorder is quite common in the totally blind who have no access to the entraining effects of light. Without the entraining effects of light the sleep in these patients becomes chaotic following the body's intrinsic circadian rhythm of 24.5 hours. Melatonin is usually used first line for both circadian rhythm sleep disorders. In delayed sleep phase disorder the addition of a light box can be supplied to patients by the Sleep Disorders unit.
Dose & route of administration:	2mg Melatonin modified release (Circadin®) 30-60 minutes before bedtime, after food. Occasionally dose may be titrated by the sleep disorders centre to a maximum of 4mg nocte.
Duration of treatment	Lifelong, if effective and tolerated
Criteria for stopping treatment	▪ Significant adverse drug reaction ▪ Lack of efficacy – i.e. if no sleep benefit is seen following 2 weeks use ▪ At request of patient
Monitoring Requirements including frequency:	**Consultant:** Review 24 weeks after initiation to assess efficacy, then Follow up every 6 – 12 months to ensure continuing benefit of melatonin.

	GP: No specific monitoring required beyond usual GP care
Follow up arrangements	Consultant: Follow up every 6 – 12 months to ensure continuing benefit of melatonin GP: No additional follow up required beyond usual GP care
Practical issues including other relevant advice/information:	▪ Melatonin's metabolism is mainly mediated by CYP1A enzymes. Therefore, interactions between melatonin and other active substances as a consequence of their effect on CYP1A enzymes is possible ▪ Melatonin is generally well tolerated. Comparing the rate of patients with adverse reactions per 100 patient weeks, the rate was higher for placebo than Circadin. The most common adverse reactions were headache, nasopharyngitis, back pain, and arthralgia, which were common in both the Circadin and placebo treated groups. ▪ Circadin may cause drowsiness so should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety ▪ No clinical data exist concerning the use of Circadin in individuals with autoimmune diseases. Therefore Circadin is 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 should not take this medicine. NB: for full details of adverse effects and drug interactions refer to latest Summary of Product Characteristics
Information provided	Melatonin PIL (see appendix 1)
Evidence Base for treatment and Key references:	See appendix 2.

Guy's and St Thomas' NHS
NHS Foundation Trust

Use of melatonin in sleep disorders

The leaflet aims to answer your questions about taking melatonin to treat your sleep disorder. If you have any questions or concerns, please speak to a doctor or nurse caring for you.

What is melatonin?

Melatonin is a hormone, which is released by the body during the hours of darkness. It is involved in the promotion of sleep and the regulation of the human body clock. This effect has led melatonin to be used as a medicine to treat sleep disorders that involve disruption of the body clock, including circadian rhythm disorders and rapid eye movement sleep disorders.

The use of melatonin for these conditions is unlicensed. This means that although the manufacturer of the medicine has not specified it can be used in this way, there is evidence that it works to treat these particular conditions. This is why it is important for you to read **Unlicensed medicines – a guide for patients**, which has more information about this subject. There is also further information in the manufacturer's leaflet.

How do I take the medicine?

The usual dose is one 2mg tablet of modified-release melatonin (Circadin®) every night. It is usually taken 30–60 minutes before bedtime. Always follow the instructions you have been given.

What should I do if I forget to take the medicine?

If you have forgotten to take the dose before you fall asleep do not take an extra dose the following evening.

Are there any side effects?

The following are examples of some of the side effects reported by patients taking melatonin. For further **information on side effects, please see the manufacturer's leaflet that comes with the medicine.**

Side effect (What is it?)	What should I do if it happens?
Uncommon	
Head is pounding and painful (headache)	It is safe to take ibuprofen and/or paracetamol.
Reduced body temperature	Contact your GP before taking the next dose.
Itching	Try applying a moisturising cream or anti-itch cream.
Rare	
Fast heart beat (palpitations)	Contact your GP before taking the next dose.

If any of the side effects persist or become a problem, contact your GP/consultant or pharmacist.

showing we care

Is there anything else I need to know?

Melatonin rarely causes problems with other medicines. Check with your GP, Consultant or pharmacist if you have any worries. If you are buying medicine over-the-counter from a pharmacy always mention that you have been prescribed melatonin. It is safe to take ibuprofen or paracetamol with this medicine. Advice should be sought when purchasing herbal or homeopathic remedies.

This medicine should be stored at room temperature away from direct sunlight, heat and out of reach of children. The expiry date is printed on the container. Do not use the medicine after this date. The remainder should be returned to your local pharmacy to be discarded.

Where can I get a repeat prescription?

Your GP will give you a repeat prescription for melatonin, which you can take to your local community pharmacy for supply.

Who can I contact for more information?

If you have any questions or concerns about your sleep disorder please contact the Sleep Disorder Centre on 020 7188 3430 (9am – 5pm).

Pharmacy medicines helpline – For information about any medicines that you have been prescribed at Guy's and St Thomas' hospitals, you can speak to the staff caring for you or call our helpline. **t:** 020 7188 8748 10am to 12 noon and 2pm to 4pm, Monday to Friday.

Patient Advice and Liaison Service (PALS) – To make comments or raise concerns about the Trust's services, please contact PALS. Ask a member of staff to direct you to the PALS office or:
t: 020 7188 8801 at St Thomas' **t:** 020 7188 8803 at Guy's **e:** pals@gstt.nhs.uk

Knowledge & Information Centre (KIC) – For more information about health conditions, support groups and local services, or to search the internet and send emails, please visit the KIC on the Ground Floor, North Wing, St Thomas' Hospital.
t: 020 7188 3416

Language support services – If you need an interpreter or information about your care in a different language or format, please get in touch using the following contact details.
t: 020 7188 8815 **fax:** 020 7188 5953

Guy's and St Thomas' NHS Foundation Trust
St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH Guy's Hospital, Great Maze Pond, London SE1 9RT
Switchboard: 020 7188 7188 www.guysandstthomas.nhs.uk
 Acute/PPG 2919 Review by: Nov 2013

Appendix 2: BACKGROUND TO THE CONDITION AND SUMMARY OF CLINICAL TRIAL DATA[2-7]

Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin. Physiologically, melatonin secretion increases soon after the onset of darkness, peaks at 2 – 4 am and diminishes during the second half of the night. Melatonin is associated with the control of circadian rhythms and entrainment to the light-dark cycle. It is also associated with a hypnotic effect and increased propensity for sleep.

There is trial evidence to support the use of melatonin in REM sleep behaviour disorder and circadian rhythm sleep disorders.

REM sleep behaviour disorder (RBD)

- The review by Gagnon *et al* (2006) 2 summarised 3 studies assessing the effects of melatonin on RBD.
    - The study by Kunz and Bes (1999) was a 6-week open-label study (n = 6) in which patients were given 3mg melatonin 30 minutes before bedtime. Within 1 week, 5 patients reported improvement in RBD – the non-responding patient was not compliant with the timing of melatonin administration. After discontinuation of melatonin, RBD symptoms returned in 4-5 weeks for two patients and in 3-7 months for two other patients. One patient noticed the return of nocturnal behaviour after 22 months. It is not clear if patients continued treatment with other hypnotics after the study ended.
    - The study by Takeuchi *et al.* (2001) was an open-label study (n = 15) of unknown duration. Patients were given 3, 6 or 9mg of melatonin 30 minutes before bedtime, according to the degree of their clinical symptoms. Thirteen patients and their partners noticed a suppressing effect on problem sleep behaviours after melatonin administration (1 with 25% less vigorous sleep behaviours, 9 with 50% less and 3 with 75%).
    - The study by Boeve *et al*. (2003) reported the effects of melatonin, for RBD, in 14 patients over a period of 18 months. The dose ranged from 3mg -12mg and the mean duration of follow-up was 14 months. Ten patients experienced marked improvement in RBD symptoms, of whom five were also using 0.5-1.0mg of clonazepam nightly.
- A study by Anderson and Shneerson (2009) included two patients who both found melatonin (10mg) effective for RDB, one after treatment failure with clonazepam and one as first-line treatment because of co-existent cognitive impairment and mild obstructive sleep apnoea.3

Circadian rhythm sleep disorders (CRSDs)

Delayed sleep phase disorder (DSPD) is characterised by a stable sleep schedule that is substantially later than the c onventional or desired time. Patients with DSPD have sleep onset insomnia and extreme difficulty arising when they attempt to conform to a conventional work schedule or other social demands.

- Melatonin administration in the afternoon or evening, during the phase advance portion of the melatonin PRC, would be expected to shift rhythms earlier, thereby correcting a pathological phase delay. This hypothesis was supported in an early study of limited sample size (N = 8), (level 2). In a large (N = 61), open-label study, those receiving 5 mg of melatonin given at 22:00 for six weeks reported significant benefit, but also a high rate of relapse when treatment was discontinued.
- In a double-blind, cross-over study, DSPD patients (N = 20) were treated with 5 mg melatonin or placebo, taken between 19:00 and 21:00 (time chosen by each patient) for four weeks. Melatonin treatment significantly reduced sleep onset latency as determined by polysomnography (PSG). However, PSG-determined total sleep time (TST) was not increased, nor were self-reported measures of daytime alertness improved.
- A double-blind study tested two doses of melatonin (0.3 and 3 mg) vs. placebo. Circadian phase using dim light melatonin onset (DLMO) and core body temperature minimum (CBTmin.) was measured before and after treatment. Treatment was administered between 1.5 and 6.5 hours prior to the DLMO for four weeks. Both doses advanced DLMO and CBTmin; the earlier the melatonin was administered relative to DLMO, the larger the phase advance, consistent with the reported melatonin phase response curve (PRC).
- The American Academy of Sleep Medicine concluded that the evidence is quite strong that melatonin, timed to promote a corrective phase advance, is an effective treatment for DSPD. Determining the optimal parameters for scheduling and dosing will require more study.

- A DARE systematic review 6 concluded that there is limited support for melatonin use in people with DSPD and limited evidence to support its use in primary insomnia.

Irregular sleep wake rhythm (ISWR) is characterised by the relative absence of a circadian pattern to the sleep-wake cycle. Total sleep time ma y be comparatively normal, but instead of being consolidated into distinct bout or bouts, sleep times are shortened, and in extreme cases, almost randomly distributed throughout the day and night. In otherwise healthy people, the condition may be a result of very poor sleep hygiene; however, ISWR is commonly associated with neurological impairment, such as mental retardation in children and dementia in older adults.

- One study reported some success in treating sleep disturbances in children with presumed ISWR and severe psychomotor retardation. However, this study was poorly controlled and employed a small sample size. Another study reported an incomplete, but significant benefit in an open label trial of melatonin (2 to 20 mg) given at bedtime to neurologically multiply-disabled children with chronic sleep wake cycle disorders. A later report compared controlled release melatonin (CR) to immediate release (IR) (2 to 12 mg) in a similar population; the CR formulation was found to be superior to IR for sleep maintenance. A trial of melatonin which sought to improve sleep timing and quality in girls with Rett syndrome and associated mental retardation, was negative.
- A double-blind, randomised, crossover trial with 44 participants with diagnosis of dementia and comorbid sleep disturbance compared two weeks of slow release melatonin (6 mg) versus placebo. Only 25 out of 44 patients completed the trial. Melatonin had no effect on actigraphically measured total time asleep, number of awakenings, or sleep efficiency. A large multicenter trial, randomised 157 Alzheimer dementia patients with insomnia and daytime sleepiness to melatonin 2.5 mg m/r, melatonin 10 mg, or placebo. The protocol consisted of 2 to 3 weeks of baseline measurement, 8 weeks of treatment, and 2 weeks placebo washout. monitored sleep was not significantly improved with either melatonin dose or placebo.
- The American Academy of Sleep Medicine concluded that the available data do not support the use of melatonin for treating ISWR, at least in association with Alzheimer disease. However, the impact of smaller doses of melatonin and that of the emerging melatonin receptor agonists has yet to be determined.

Free running disorder (FRD) develops when normal (unaffected) subjects are maintained in an inpatient research environment devoi d of time cues. The condition is very rare in normally sighted people, but quite common in the totally blind who have no access to the entraining effects of the light/dark cycle.

- There were four case reports of successful treatment of sighted FRD with melatonin administered around the hour of the desired bedtime when it would be predicted to cause a phase advance. The most common dose was 3 mg and the duration of treatment ranged from one month to six years.
- The American Academy of Sleep Medicine concluded that although the studies are limited by the rarity of this condition, both appropriately timed bright light exposure and melatonin administration have shown to entrain **sighted** patients with FRD.
- In addition to several positive case reports, there have been two small single-blind, placebo-controlled melatonin treatment trials demonstrating successful entrainment of free-running rhythms in totally blind people. In one study, 3 of 7 subjects entrained to 5 mg of melatonin given for 35-71 days at 21:00. In the other study, 6 of 7 subjects entrained to 10 mg given at the usual bedtime for 3 to 9 weeks. In this study, three of the subjects were given a 10 mg dose that was gradually stepped-down every other week to 0.5 mg. Melatonin treatment on this step-down dosing schedule maintained entrainment, and free-running rhythms recurred after the cessation of treatment. Subsequently, these same subjects were successfully entrained with 0.5 mg de novo. The subject who failed to entrain in the initial trial to 10 mg was subsequently entrained with a 0.5 dose. The effectiveness of the lower dose was attributed to its selective activity on the advance zone of the melatonin phase response curve with no “spillover” to the delay zone. In another recent trial, the 0.5 mg dose entrained 6 of 10 subjects. In summary, the evidence is compelling that melatonin can entrain the majority of totally blind patients with FRD. Furthermore, a *physiological* dose (0.5 mg) appears to be as effective as a *pharmacological* dose (5 to 10 mg), and in some cases, more effective.
- The American Academy of Sleep Medicine concluded that appropriately timed melatonin, in doses from 0.5 mg to 10 mg, have been shown to entrain **totally blind** people who have FRD. The effective dose may be even less than 0.5 mg (the dose that approximates a physiological plasma concentration). Treatment must be sustained or relapse will occur. Entrainment may not occur for weeks or months after initiating treatment, depending on the phase of the patient's rhythm when treatment is started and the period of the patient's free-running rhythm.

References

1. Melatonin SPC: http://www.medicines.org.uk/EMC/medicine/20878/SPC/Circadin+2mg+prolonged-release+tablets/
2. Lundbeck Limited (May 2009) Summary of Product Characteristics, *Circadin 2mg prolonged-release tablets*.
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7. MacMahon KM *et al.* (2008) A systematic review of the effectiveness of oral melatonin for adults (18 to 65 years) with delayed sleep phase syndrome and adults (18 to 65 years) with primary insomnia. [Abstract 12006006046] Database of Abstracts of Reviews of Effects (DARE)