SHARED CARE GUIDELINES ON MELATONIN FOR SLEEP DISORDERS/DIFFICULTIES IN CHILDREN UNTIL THEIR 18TH BIRTHDAY (NELFT)

DOCUMENT TO BE SCANNED INTO ELECTRONIC RECORDS AND FILED IN NOTES

Patient Name : **Date of Birth:** **NHS No:**

Name of Referring Consultant: **Contact number:**

INTRODUCTION – Indication and Licensing

1. The treatment of insomnia in children with sleep disorders, is to be initiated by specialist secondary care (experienced psychiatrists for CAMHS or experienced community paediatricians only)

2. Insomnia is a common problem for children with sensory deficits, some learning disabilities and childhood psychiatric disorders such as autistic spectrum disorder and ADHD.

3. Insomnia and other non-respiratory sleep disorders in children and adolescents are a widespread problem, with a higher prevalence in children with neurodevelopmental or psychiatric co-morbidities. Although non-drug treatments, such as behavioural therapy can be extremely effective in some forms of paediatric insomnia, clinical experience and studies with children with neuropsychiatric disorders indicate that these patients have lower response rates to behavioural therapy. There are no drugs licensed for the treatment of sleep disorders in children in the UK.

BioChemical Information

4. Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone produced by the pineal gland during the dark hours of the day-night cycle. The pineal gland produces it in a circadian manner, in response to darkness. The link with circadian rhythms has led to its use in the treatment of sleep disorders underpinned by learning disability, autistic spectrum disorders, and ADHD. Its use is supported by NICE in their Clinical Guideline on the diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in adults and children. Within that Guideline it is stated that melatonin may be considered for children and young people with CFS/ME who have sleep difficulties, but only under specialist supervision.

Current Status

5. Melatonin is classified as a medicine in the UK, and is currently unlicensed for these indications in children and adolescents. In contrast, it is readily available to purchase in some countries, e.g. USA.

6. There are no licensed products of Melatonin in the UK for the treatment of childhood insomnia. Circadin® is a sustained release formulation of melatonin that is licensed in the UK for the treatment of primary insomnia in adults aged 55 years and over.

7. A prolonged release formulation of melatonin (Circadin®) was licensed in the UK in June 2007 as a short term treatment of primary insomnia characterised by poor quality sleep, but only in patients aged 55 years or over. The safety and efficacy of Circadin® in children aged 0 to 18 years has not yet been established. No data are available. Its use in this age group will be off-label. Unlicensed preparations of melatonin are available from several pharmaceutical companies on a named patient basis – it is believed that there are at least 50 melatonin preparations that are either being imported into, or manufactured in, the UK. In the US it is freely available to purchase as a food supplement.

Studies on Usage

8. There is at least one systematic review, two meta-analyses and several subsequently published randomised controlled trials which assess the safety and efficacy of melatonin in children and adolescents. Although somewhat limited by trial size, heterogeneity and specificity, typically these pieces of research support the use of melatonin in that they show it has some beneficial effect in measures of

sleep efficiency. Although the evidence base for melatonin is limited, it is actually more substantial than that available to support the use of any alternative hypnotic in this population.

9. In practice, the use of melatonin for the treatment of paediatric sleep-wake cycle disorders is widespread. There are a number of published trials, although these are often small and of short duration. However there is some long term data from NICE Advice ESUOM2. The long-term follow-up study (Hoebert et al. 2009[16]) obtained data on 94 of the 105 (89.5%) participants who received unlicensed melatonin or placebo during the study by van der Heijden et al. (2007)[14]. The mean follow-up time was 3.7 years. Mean age at the start of melatonin treatment was 8.7 years and 12.4 years at follow-up. After the RCT by van der Heijden et al. (2007), all children were offered melatonin, breaking the randomisation. At follow-up, 61 (64.9%) children used melatonin daily, 11 (11.7%) used it occasionally (in most cases only using melatonin when they could not sleep), and 22 (23.4%) were not using melatonin. Parental satisfaction with melatonin was high with 87.8% of parents expressing the opinion that "melatonin is an effective therapy for the sleep onset problems of my child", 70.8% that "melatonin improved daytime behaviour of my child" and 60.9% that "melatonin improved the mood of my child". During the treatment period, 67 children (71.3%) temporarily discontinued melatonin. The effect of this in most of the cases (92.3%) was a delay in sleep onset time.
Children with or without ADHD treated with melatonin have been shown to fall asleep earlier and sleep for longer when compared to controls. Generally no significant change in behaviour or attention has been demonstrated. It would appear that there is wide variability in response. Melatonin may be most effective in those children whose sleep patterns indicate that their circadian rhythm is disrupted, and in whom sleep hygiene methods have been ineffective.

Indications for Usage

10. For use in children of at least 1 year of age with neurodevelopment disability, autism, visual impairment or neuropsychiatric disorders and chronic sleep disturbance, including chronic fatigue syndrome, where both:

a. 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
b. Sleep hygiene / behavioural measures had a reasonable trial and failed.

Children are typically of school age. There may be other causes of these symptoms e.g. depression or anxiety. Other approaches to therapy can be considered; however, melatonin is not known to cause harm.

PATIENT PATHWAY- *brief explanation of why planned arrangements for prescribing and monitoring between primary and secondary care are appropriate*

11. This document outlines ways in which the responsibilities for managing the prescribing of melatonin for children with sleep disorders are shared between the specialist and general practitioner (GP). GPs are requested to participate in this process. If the GP is not confident to undertake these roles initially further advice and support will be available from the Specialist Prescriber. Clinical responsibility lies with the clinician who signs the prescription. **If a specialist asks the GP to prescribe this drug, the GP should reply to this request within two weeks. The request will be faxed a second time and a follow up phone call, if there is no response it will be assumed that the shared care protocol has been agreed upon.**

12. Sharing of care requires communication between the specialist, GP and child/parent or carer. The intention to share care should be explained to the child /parent by the doctor initiating treatment. It is important that parents and children are consulted about treatment and are in agreement with the process.

Withdrawal Recommended

13. Specialists should review the need for continued treatment at each outpatient or community team appointment (at least every 6 months) and advise the GP of continuation, changes or discontinuation of treatment.

ORAL DOSE AND ADMINISTRATION

Dosage and Administration

Age	Oral dose	Maximum dose
1 year onwards	Initial dose 2mg (given 30-60 minutes before bedtime). In the absence of improvement after 1-2 weeks, the dose is increased by 2mg incrementally according to response.	12mg/day

a. For children waking during the night, the same dose or a smaller dose can be repeated during the night. The 2mg SR Circadin® tablet can be halved using a tablet cutter and it will retain its slow release characteristics[17].
b. For children with difficulties swallowing, the tablet can be crushed to a fine powder and mixed with water or given with cold soft food such as a teaspoon of yoghurt or jam. Use a small amount of food to ensure the full dose is taken. The prescription should state that the medication is to be crushed prior to administration.
c. For administration via an enteral feeding tube, the tablet can be crushed to a fine powder and added to 15 - 30ml of water and mixed well. This should be drawn into a 50ml oral syringe and administered taking care to rinse the mortar/tablet crusher with water and administering the rinsings also. The feeding tube should be flushed with 30ml water prior to and post drug administration.
d. NOTE: crushing the MR tablet will mean that it is no longer modified release.
e. Special order liquid medicines or capsules (all unlicensed brands) are unlicensed and should ONLY be used where absolutely necessary. The prescription must state the brand to be used.
f. A drug holiday should be introduced at least annually to assess the continued need for treatment. This could take place a month before the annual review with the patient and / or the parent keeping a sleep diary. The outcome of any drug holiday must be recorded in the patient's notes

MONITORING STANDARDS FOR MEDICATION AT NELFT

Administration and Supply

a. The patient and carer must be advised that this is an unlicensed use or an unlicensed product which limits the information that is available about effectiveness and safety
b. The patient must be given an appropriate Patient Information Leaflet (generic unlicensed medication leaflet) on unlicensed medication at the point of initiation.
c. Supply will be by prescription only for the individual patient by a Doctor or non-medical prescriber for the individual patient
d. When the patient is stable the GP should be contacted to request prescribing

KEY ADVERSE EFFECTS & ACTIONS

14. The most common adverse reactions were headache, nasopharyngitis, back pain, and arthralgia, which were common, by MedDRA definition, in both the Circadin and placebo treated groups.There are also concerns that melatonin may adversely affect seizure control, gonadal development and asthma control and at present there is no robust data available to support or refute any of these concerns.

15. Melatonin is generally well tolerated, but long term side effects have not been evaluated. Increased seizure activity has been reported in patients with epilepsy but there is also anecdotal evidence that seizure activity improves as a result of improved sleep. Much of the clinical trial data with melatonin does not report an increase in seizure frequency, but data must be treated cautiously due to the short term nature, size, and heterogeneous nature of the populations studied. Until more is known prescribers need to approach melatonin use in children with epilepsy highly cautiously and be alert for alterations in seizure activity.

16. Concern has been expressed that exogenously administered melatonin could, at least theoretically, adversely affect gonadal development if used in children. 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 included in this review, none reported an association between melatonin and delayed onset of puberty, but most studies of melatonin have been short term, and longer term follow-up will be needed to fully address this concern.

17. Endogenous serum melatonin concentration is elevated in nocturnal asthmatic patients. Although the clinical trial data presented here does not indicate an increase in asthma symptoms, melatonin should be used with caution in this group. Most commercial melatonin is synthesized in the laboratory. However, in rare cases it has been derived from animal pineal gland. Melatonin from animal sources should be avoided due to the possibility of contamination.

18. Adverse events, interactions and precautions for the licensed Circadin™ preparation can be found in its SPC. This is only licensed for (and has only been adequately tested in) adults aged 55 years and above with primary insomnia, therefore the information presented in the SPC cannot be presumed to apply to paediatric patients with neurodevelopmental disorders (NDD).

Overdose

19. Administration of daily doses of up to 300mg of melatonin without causing clinically significant adverse reactions has been reported in the literature.
If overdose occurs, drowsiness is to be expected. Clearance of the active substance is expected within 12 hours after ingestion. No special treatment is required.

Contra-indications; Special Warnings and Precautions for Use

a. Hypersensitivity to the active substance or to any of the excipients.
b. Melatonin may cause drowsiness.
c. No clinical data exists concerning the use of melatonin in individuals with autoimmune diseases and so use is not recommended in this group of patients.
d. Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency (this is when the body is unable to digest milk and milk products due to a lack of an enzyme) or glucose-galactose malabsorption should not take Circadin brand melatonin (contains lactose).

Interactions

20. From case reports in the literature, clinical experience and theoretical principles it has been suggested that interactions may occur with anticoagulant/antiplatelet drugs, antidiabetic agents, benzodiazepines/ CNS depressants, carbamazepine and rifampicin, cimetidine, contraceptives, flumazenil, fluvoxamine, immunosuppressants, quinolones, nifedipine, verapamil and calcium channel blockers in general, verapamil antipsychotics, propofol, caffeine & 5- or 8-methoxypsoralen (5 and 8-MOP). Cigarette smoking may decrease melatonin levels. 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.

21. Interactions for the licensed Circadin™ preparation can be found in its Summary of Product Characteristics (SPC). www.medicines.org.uk

For comprehensive information please refer to the current British National Formulary and Summary of Product Characteristics.

PREGNANCY AND BREAST FEEDING

If is recommended that the patient should not become pregnant whilst on the drug-add a statement that both men and women will be counselled about contraception and what to do if pregnancy occurs. The counselling should be documented in the patient notes.

For comprehensive information please refer to the current British National Formulary and Summary of Product Characteristics.

SHARED CARE

22. Shared care guideline: is a document which provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital specialist, GP and the patient and also sets out responsibilities for each party. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Intrinsic in the shared care agreement is that the prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use.

Consultant

1) Diagnosis. A thorough history should always be taken and a sleep diary used if there is any doubt about the extent of the problem.
2) Initiation of treatment by an experienced community psychiatrist or paediatrician for CAMHS, Learning Disabilities or paediatrics, who should first discuss the treatment options with the patient, their parent(s) and carer(s), including the unlicensed nature of melatonin, the need for shared care (once dose stabilised), and obtaining appropriate consent to treatment.
3) **Initiate treatment with melatonin only if agreed.**
4) Advice to the patient and carer to follow sleep hygiene measures (bedtime and wake up routine, avoidance of daytime sleep) and to continue the sleep diary throughout treatment with Melatonin, if practicable.
5) The initiating prescriber will continue to prescribe and supply until stability is established (at least 1 month)

6) Written notification to the GP when the Melatonin is initiated, and again when the patient is stabilized to ask the GP whether he is willing to participate in the ongoing prescribing and general care as outlined in this continuing care guideline. A copy of the guideline should be sent with the letter.
7) Outpatient appointments at least annually, and regular appointments with the community teams or paediatric support team. At these appointments the efficacy of Melatonin will be reassessed, and discontinued or reviewed as indicated.
8) Report any suspected adverse drug reactions (ADRs) to the Medicines and Healthcare products Regulatory Agency (MHRA) via the yellow card scheme.
9) When appropriate, undertake periodic treatment withdrawals (drug holidays), or advise the GP in writing how and when to undertake them.
10) Promptly communicate any changes, recommendations, outcomes or other important information to the GP.
11) Provide advice to the GP or patient if they have clinical queries relating to the condition or use of melatonin.

General Practitioner

1) The GP is responsible for the general health and well-being of the patient.
2) If he/she considers that the patient should be reviewed he/she should contact the initiating prescriber or the CAMHS or paediatric team, but will continue to prescribe until the reassessment has taken place (unless an adverse effect has occurred). Max review 6 months.
3) Continuation of melatonin without specialist review is not recommended.
4) Prescribe melatonin once the patient is on a stable dose.
5) Communicate any problems to the Specialist looking after the patient.
6) Only ask the Specialist to take back the prescribing should unmanageable problems arise.
7) Ensure compatibility of melatonin with concomitant medication.
8) Report any suspected adverse drug reactions (ADRs) to the Medicines and Healthcare products Regulatory Agency (MHRA) via the yellow card scheme.
9) Inform consultant if unable to take on shared care.

PCT

1) To provide feedback to trusts via Trust Medicines Committee.
2) To support GPs to make the decision whether or not to accept clinical responsibility for prescribing.
3) To support trusts in resolving issues that may arise as a result of shared care.

Patient/ Carer

1) Ensure they have a clear understanding of the treatment.
2) Take/give the melatonin as directed.
3) Share any concerns in relation to treatment with the Specialist, GP or pharmacist.
4) Report any adverse effects or warning symptoms to the Specialist, GP or pharmacist whilst taking/giving the medication.
5) Attend booked appointments for review and monitoring of therapy.

Costs

NHS Cost and Choice of Product

With the exception of the Circadin® brand, melatonin is not licensed in this country, therefore a prescription for melatonin can be met by any product of any price, at the discretion of the dispensing pharmacy. This could prove to be very expensive. Prescribers are strongly advised to specify a brand or a manufacturer. The MHRA advice is to prescribe in the following order of preference (see below):

i. If there is a licensed product available it should be used, even if it is for an unlicensed use. **This means Circadin® 2mg prolonged release tablets.** A "special clinical need" letter should still be provided.
ii. There are a number of unlicensed UK specialist manufacturers and the import of unlicensed products, particularly from the USA, where melatonin is classed as a food supplement. The standards of manufacture and quality control will be unpredictable. There is likely to be a time delay, and the cost is unspecified. A "special clinical need" letter should still be provided.
iii. On the rare occasion a liquid is essential Melatonin oral solution 1mg/ml should be prescribed (note cost).

Product	Manufacturer	Strength/form	Pack size	Price (Oct 09)
Licensed product but unlicensed use - TO BE USED UNLESS THERE ARE GOOD REASONS WHY IT WILL BE UNSUITABLE. **It can be crushed if necessary** (as detailed in dosage & administration)				
Circadin®	Flynn Pharma	2mg slow release tab	30	£15.39
Melatonin oral solution available from special order manufacturers or specialist importing companies in the UK		1mg/ml oral solution	200ml	£80.48

RESOURCES AVAILABLE

Summary of product characteristics. Circadin®. Accessed via: https://www.medicines.org.uk/emc/medicine/25643
Patient information leaflet. Circadin®. Accessed via: http://www.medicines.org.uk/emc/medicine/27475
British National Formulary for Children 2014-2015. *Accessed via: https://www.medicinescomplete.com/mc/bnfc/current/*
Royal College of Psychiatry www.rcpsych.nhs.uk
Taylor D, Paton, C, Kapur S. The Maudsley Prescribing Guidelines in Psychiatry 11th edition, Wiley-Blackwell, 2012.
Bazire, S. Psychotropic Drug Directory. Lloyd-Reinhold Communications LLP, 2014.
NHS Direct accessible for patients www.nhsdirect.nhs.uk
NICE Clinical Guidelines 53: Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy) (August 2007). Accessed via: http://www.nice.org.uk/guidance/cg53/evidence
NICE Advice ESUOM2: Sleep disorders in children and young people with attention deficit hyperactivity disorder: melatonin (January 2013). Accessed via: http://www.nice.org.uk/advice/esuom2
Stockleys Drug Interactions. Accessed via MedicinesComplete: https://www.medicinescomplete.com/mc/stockley/current/interactions.htm?q=melatonin&searchButton=+
Data on file – Flynn Pharma Ltd. July 2012. In-vitro Release (Dissolution) of Circadin® from Intact, Divided and Crushed Melatonin Tablets

If you would like information about medicines used in mental health services, please click on the link below. This will take you to the NELFT section of a website called Choice and Medication.
Go to the Choice and medication website.
The information on this website can help you to make informed decisions about medication. Use this site on your own or use it together with your family or someone you care for or your doctor, nurse or pharmacist. Medications website's full link:
http://www.choiceandmedication.org.uk/nelft/

NELFT - For Back-up Advice and Support

Chief Pharmacist or the local Consultants can be contacted for advice.

Ms.Heather Walker	Chief Pharmacist	03005551200
Dr. Trudie Rossouw	Consultant child & adolescent Psychiatrist	03005551155
Dr. Leon Wehncke Alexander	Consultant child & adolescent Psychiatrist	03005551155
Dr.Yvonne Treffurth	Consultant child & adolescent Psychiatrist	03005551035
Dr.Skirma Povilenaite	Consultant child & adolescent Psychiatrist	03005551035
Dr. Ragini Bahry	Consultant child & adolescent Psychiatrist	03005551182
Dr. Ralph Littlejohn	Consultant child & adolescent Psychiatrist	03005551182
Dr.Manas Sarkar	Consultant child & adolescent Psychiatrist	03005551124
Dr. Hena Vijayan	Consultant child & adolescent Psychiatrist	03005551124

Dr.Colin Welch	Consultant child & adolescent Psychiatrist	03005551247
Dr. Eparu Iuliana	Consultant child & adolescent Psychiatrist	03005551247

Refer to the BHR CCG's website to obtain the latest version of this guideline

SHARED CARE GUIDELINES ON
MELATONIN FOR SLEEP DISORDERS/DIFFICULTIES IN CHILDREN (NELFT)

SHARED CARE AGREEMENT LETTER

Name of GP …… Address …….
……..……..
……..……
..…….

Dear GP

Re: Patient's Name……..……

Date of Birth…….……

Hospital Number……..…….

Indication for ……..……

Route…….(Oral)

Dose……..mg per day.

Enclosed is a copy of the shared care guidelines for [Drug Name] to be retained in the patient's notes.
Should you agree to shared care, we will send a letter containing the details of the patient's treatment plan, the dose to be prescribed and all relevant blood results.

Please sign below and return this letter to the Hospital Specialist if you agree to the shared care arrangements for this patient.

Many thanks

Hospital Specialist GP

Signature…….. Signature……...

Name ……..…….. Name ……...

Date…….. Date……..…….

If you are not taking on shared care for this patient please state the reason why and return this letter to the Hospital Specialist.
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