THE
THE DONCASTER & BASSETLAW PLACE

Shared Care Guideline
For
Melatonin in the Management of Sleep Disorders in Children and Young People with Neurodevelopmental Disorders and for adults aged over 18 with a learning disability (off-label)

For Bassetlaw: This Shared Care Guideline ONLY applies for patients under the care of DBTHFT paediatrics and RDaSH.

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Statement of Purpose

This shared care guideline (SCG) has been written to enable the continuation of care by primary care clinicians of patients initiated on melatonin by the secondary care specialists (consultant paediatricians, psychiatrists, neurologists), where this is appropriate and, in the patients', best interests. Primary care will only be requested to take over prescribing of melatonin within its licensed indication unless specifically detailed otherwise below.

1. This is guidance on the management of a condition not a commissioning arrangement

Shared care guideline for melatonin in the Management of Sleep Disorders in Children and Young People with Neurodevelopmental Disorders, and in adults aged over 18 with a learning disability (off-label use)

Responsibilities of specialist clinician

- To discuss benefits and side effects of treatment with the patient/carer and obtain informed consent, in line with national guidance. This is particularly important for unlicensed products.
- To discuss the importance of sleep hygiene and regular sleep routine.
- To provide patient / carer with contact details for support and help if required; both in and out of hours
- To initiate melatonin in appropriate patients
- To explain the unlicensed nature of melatonin
- To conduct baseline monitoring to include height, weight
- To prescribe the first month's supply or until patient stable
- To contact patient's GP to request prescribing and monitoring under shared care and send a link to or copy of the shared care guideline.
- To advise the GP regarding continuation of treatment, including the duration of treatment
- To discuss any concerns with the GP regarding the patient's therapy
- To review the patient in clinic, regularly until optimum dose is established and then 6 -12 monthly reviews.
- To consider reduction or stopping of the medication for a trial period if considered appropriate, this is usually after a period of stability for the child and their environment of about six months.
- The patient to normally remain under the specialists' care but if ongoing specialist co-ordination of the patient's care is not required the specialist must provide access to advice and intervention of that specialist in a timelier manner than via a new referral.

- To review if a child, as they move towards the age at which they will be discharged from the Paediatric pathway to determine on-going need:
  - To facilitate the cessation of drug therapy at this stage if clinically possible
  - To discuss with parent/carer the limitations of the duration of shared care agreement and ensure they understand that treatment will not be provided by the GP once the child has been discharged from the Paediatric pathway
  - To provide guidance to the parent/carer on lifestyle and sleep management should treatment be ceased (if applicable)

Responsibilities of the primary care clinician

- To refer appropriate patients to secondary care for assessment
- Confirm the agreement and acceptance of the shared care prescribing arrangement and that supply arrangements have been finalised (see appendix for template letter). Or to contact the requesting specialists if concerns in joining in shared care arrangements,
- To report any serious adverse reaction to the appropriate bodies e.g.: MHRA and the referring specialist
- To continue to prescribe for the patient as advised by the specialist
- Ensure monitoring as indicated in monitoring section below
- To inform the specialist if the patient discontinues treatment for any reason
- To seek the advice of the specialist if any concerns with the patient's therapy
- To conduct an annual medication review or more frequent if required. In the event that the GP is not able to prescribe, or where the SCG is agreed but the specialist is still prescribing certain items e.g. Hospital only product; the GP will provide the specialist with full details of existing therapy promptly by fax (or other secure method) on request.

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- For medication supplied from another provider prescribers are advised to follow recommendations for Recording Specialist Issued Drugs on Clinical Practice Systems

Responsibilities of Patients or Carers

- To be fully involved in, and in agreement with, the decision to move to shared care
- To make ongoing efforts in maintaining sleep routine and sleep hygiene measures.
- To attend hospital and primary care clinic appointments and to bring monitoring information e.g.: booklet (if required). Failure to attend will potentially result in the medication being stopped.
- Present rapidly to the primary care prescriber or specialist should the clinical condition significantly worsen.
- Report any suspected adverse effects to their specialist or primary care prescriber whilst taking melatonin
- To read the product information given to them
- To take melatonin as prescribed
- Inform the specialist, primary care prescriber or community pharmacist dispensing their prescriptions of any other medication being taken – including over-the-counter medication.

Indications

Melatonin is a naturally occurring hormone secreted by the pineal gland in the brain in a circadian manner. It is involved in co-ordinating the body's sleep-wake cycle helping to regulate sleep through its regulation of the activity of the suprachiasmatic nucleus and sleep related brain networks. Melatonin production is suppressed by light and stimulated by darkness, a rise in serum levels precede the onset of sleep by about 90 minutes.
Neurodevelopmental disorders (NDD) include attention deficit-hyperactivity disorder (ADHD), autism spectrum disorder, Rett syndrome, intellectual deficits, visual impairment, epilepsy and brain damage. Abnormal melatonin secretion has been identified in children with NDD; this has prompted the use of melatonin therapy to treat sleep disorders in these populations.

Choice of preparation

This flow chart shows the order of preference for prescribing the different preparations. Each preparation is further discussed in the following fact pages.

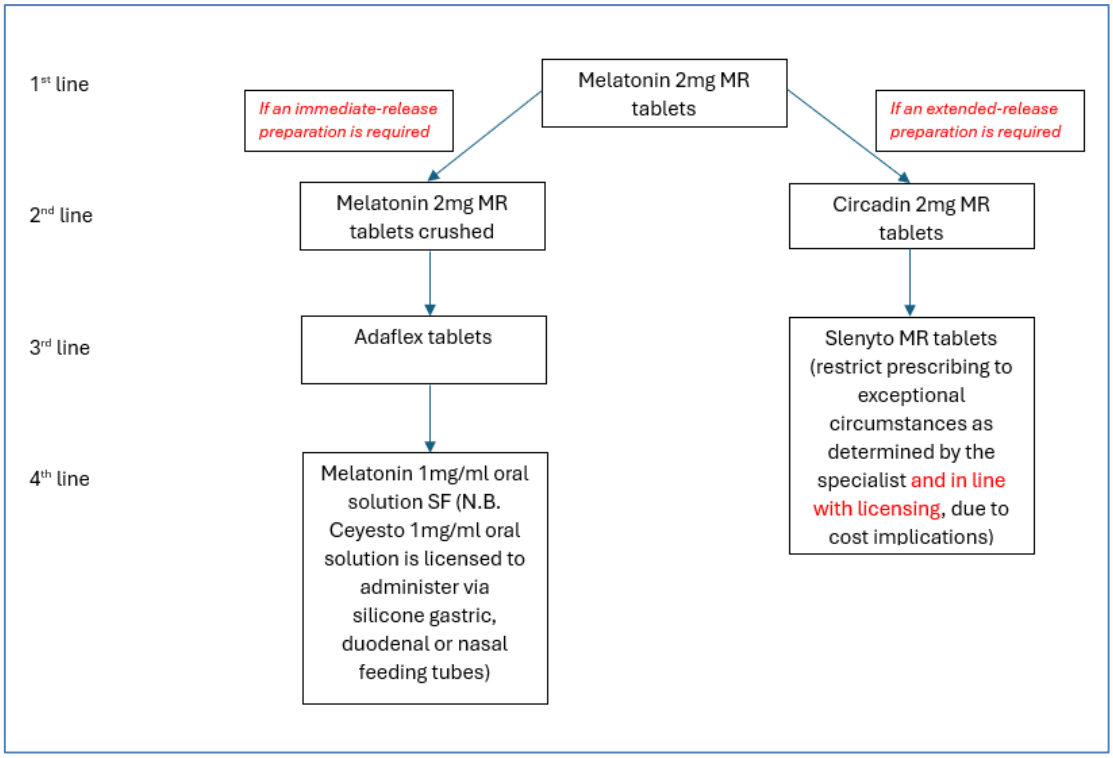
Note: This Shared Care Protocol and Proforma allows for the following, without the need for completion of a new Proforma:

- **Change of dosage within the same drug**
- **Change of formulation**

Any such changes must be initiated by the specialist and communicated to the GP in writing.

The treatment of choice for sleep disturbance is behavioural; melatonin should only be prescribed after a full trial of behavioural management has been tried and has failed to achieve satisfactory results. Environmental modification should also be ensured. Establishing a good sleep routine and maintaining sleep hygiene is important.

The NICE ESUOM2 (Evidence summary: unlicensed or off-label medicine) summarises the evidence for melatonin in children and young adults with ADHD. This concludes that there is limited evidence for melatonin use; also, that melatonin is well tolerated.



SIGN 98 reviews the assessment, diagnosis and clinical interventions for children and young people with autism spectrum disorders. This states that melatonin may be considered for treatment of sleep problems that have persisted despite behavioural interventions.

NICE NG11 (Challenging behaviour and learning disabilities: prevention and interventions for people with learning disabilities whose behaviour challenges) recommends that if medication is needed to aid sleep, then to consider melatonin.

Modified release (MR) melatonin 2mg tablet fact page (off label use):

Route of administration Oral

Formulation 2mg modified-release tablets prescribed generically.

- **Please note that in some circumstances, melatonin may need to be prescribed by brand, where it is determined to be essential by the specialist (for example, as Circadin).**

Licensing Melatonin 2mg MR tablets are licensed for the short-term treatment of insomnia in adults aged 55 years and over. Use in children would be 'off-label' (outside licensed indications). As per the MHRA, 'off-label' prescribing a UK licensed product is preferable to prescribing an unlicensed product.

Administration details The recommended starting dose is 2mg once daily, 30 to 60 minutes before bedtime. If an inadequate response has been observed, the dose can be increased to 4–6 mg once daily, and then further increased to a maximum dose of 10 mg. The lowest effective dose should be used. If recommended by a specialist, the tablets can be crushed before administration. This is all an **off-label** use.

Additional information After at least three months of treatment, the specialist should evaluate the treatment effect and consider stopping treatment if insufficient clinical effect is reached.

Thereafter, the patient should be monitored at least every six months to ensure that melatonin 2mg MR is still the most appropriate treatment.
Discontinuation attempts should be undertaken regularly, e.g. once a year

Melatonin (Circadin®) 2mg MR tablets contain 2mg of melatonin. These are formulated to circumvent the fast clearance of melatonin from the body and mimic the physiological pattern of endogenous melatonin release. The MR tablet releases melatonin over at least 8 hours with a component of immediate release as approx. 40% of total dose is released in the first hour.

MR melatonin tends to be used for problems with sleep maintenance/fragmental sleep and/or early morning awakening. Also, when there are problems with both sleep initiation and sleep maintenance/early morning awakening.

In-vitro Release (Dissolution) of Circadin® from Intact, Divided and Crushed Melatonin Tablets

Circadin (prolonged release melatonin tablets 2mg) are licensed in the UK for the short-term treatment of primary insomnia in patients aged over 55yrs. A single dose (tablet) of 2mg is approved at night-time (refer to Summary of Product Characteristics and Patient Information Leaflet) for treatment periods up to 13 weeks.

Circadin is formulated to provide prolonged release of melatonin from the tablet over the period of darkness/night, in a profile similar to the endogenous production of melatonin from the pineal gland. It is not recommended that patients break or crush the Circadin tablet as this may impact the intended release characteristics. However, several patients experience difficulties in swallowing and tablet breaking or sub-division and crushing are commonly used methods to aid dosing in practice. Unlicensed liquid preparations of melatonin are also widely used.

The in-vitro dissolution of Circadin was evaluated using the registered specification and methods, to assess the release profile of melatonin from Circadin tablets that were intact/whole, divided into quarters or crushed using a commercially available tablet crusher/breaker (Safe & Sound Pill Cutter, Crusher & Container, Paul Murray Plc)

The registered in-vitro release specification for dissolution provides a multipoint control on dissolution and sets limits after 1, 2, 4, 6 and 8 hrs. Dissolution data generated for the intact, quartered and crushed tablets are presented in the figure overleaf.
The intact Circadin tablet release profile indicates a progressively increasing dissolution and release of melatonin over an 8-hour period. Crushing the tablet effectively destroys the controlled release properties of the dosage form and near maximal release of melatonin is observed within the first hour. An intermediate dissolution profile is observed with the quartered tablet, which achieved 63% dissolution after one hour (compared with 39% for the intact tablet)

In conclusion these data indicate that minimal breaking of Circadin tablets has a limited, albeit significant impact on the intended dissolution characteristics, whereas if the tablet is crushed, the release characteristics approximate to an immediate release dose form. From a practical standpoint therefore, wherever possible, patients should be encouraged to swallow the tablet whole. Where this is not possible, halving or quartering the tablet, to aid administration might be expected to have some, but limited impact on its intended characteristics. The in vitro release from a crushed or powdered tablet is expected to provide an immediate release profile similar to that from an

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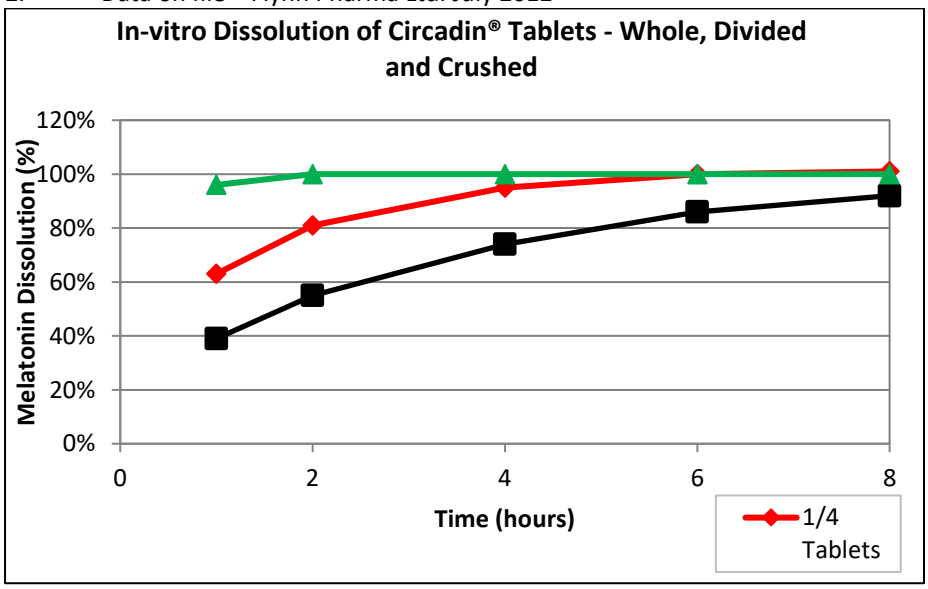
unlicensed immediate release tablet or (unlicensed) oral liquid and as such provides a viable alternative to either of these options. However, to the extent that Circadin is a licensed product, its use outside of licence (in so far as the tablet is broken or crushed) is considered preferable to an unlicensed presentation of melatonin. The prescriber should be aware that the release characteristics do not match those of the intact tablet and that this may be evident in clinical effect (when compared to the intact Circadin tablet).

References

1. Circadin SmPC last accessed October 2021
2. Data on file – Flynn Pharma Ltd. July 2012



Adaflex fact page:

Route of administration Oral

Formulation Immediate-release tablets

Licensing Adaflex® is licensed for insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.

If an immediate-release preparation is required, for example if the sleep problem is associated with sleep initiation (falling asleep), Adaflex can be used **off-label** in indications other than ADHD.

Use under the age of 6 would be **off-label.**

Administration details The recommended starting dose is 1-2mg 30 to 60 minutes before bedtime. The dose can be increased by 1mg every week, up to a maximum licensed dose of 5mg per day. The lowest effective dose should be used. In some circumstances, up to 10mg a day may be used, but this is off label.

Additional information After at least three months of treatment, the specialist should evaluate the treatment effect and consider stopping treatment if insufficient clinical effect is reached.
Thereafter, the patient should be monitored at least every six months to ensure that Adaflex is still the most appropriate treatment.
Discontinuation attempts should be undertaken regularly, e.g. once a year.

Slenyto fact page:

Route of administration Oral

Formulation Prolonged-release tablets

Licensing Slenyto® is licensed for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or neurogenetic disorders with aberrant diurnal melatonin secretion and /or nocturnal awakenings, where sleep hygiene measures have been insufficient.

Administration details The recommended starting dose is 2 mg once daily, 30 to 60 minutes before bedtime, and with or after food. If an inadequate response has been observed, the dose can be increased to 5 mg, with a maximum dose of 10 mg. The lowest effective dose should be used.

Additional information After at least three months of treatment, the specialist should evaluate the treatment effect and consider stopping treatment if insufficient clinical effect is reached.
Thereafter, the patient should be monitored at least every six months to ensure that Slenyto is still the most appropriate treatment.
Discontinuation attempts should be undertaken regularly, e.g. once a year.

Melatonin 1mg/ml oral solution SF (generic) and Ceyesto 1mg/ml oral solution fact page:

Route of administration Oral

Formulation Solution

Licensing Melatonin 1mg/1ml oral solution SF (and Ceyesto oral solution) are licensed for insomnia in children and adolescents aged 6-17 years with attention deficit hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient.

If an immediate-release preparation is required, for example if the sleep problem is associated with sleep initiation (falling asleep), or if there are swallowing difficulties, melatonin liquid can be used **off-label** in indications other than those mentioned above. Ceyesto liquid is licensed to be administered via silicone gastric, duodenal or nasal feeding tubes.

Administration details The recommended starting dose is 1 to 2 mg once a day, 1-2 hours before bedtime. The dose can be adjusted up to a licensed maximum of 5 mg per day. The lowest effective dose should be used. In some circumstances, up to 10mg a day may be used, but this is off label.

Additional information After at least three months of treatment, the specialist should evaluate the treatment effect and consider stopping treatment if insufficient clinical effect is reached.
Thereafter, the patient should be monitored at least every six months to ensure that melatonin liquid is still the most appropriate treatment.
Discontinuation attempts should be undertaken regularly, e.g. once a year.

Selection of patients

Child 1 month – 18 years. At present, there are no arrangements of continuation of shared care beyond the age of 18.

Exclusion criteria - for any additional contra-indications see below

Only those specific forms mentioned in this document are for shared care, and no other forms are available for shared care and will be retained by the initiating trust.

Contra-indications

The details below are not a complete list and the BNF and the SPC remain authoritative

- **Hepatic impairment** – avoid due to reduced clearance.
- **Renal impairment** – no information, BNF and SPC advises caution
- **Epilepsy** – monitor effect on seizure frequency in epileptic patients.
- Patients with **galactose intolerance**, the **LAPP lactase deficiency** or **glucose-galactose malabsorption** should not take melatonin.
- **Autoimmune diseases** - not recommended due to lack of clinical data.
- **Pregnancy** – not recommended for use in pregnant women or women intending to become pregnant due to lack of clinical data.
- **Breast feeding** – not recommended as is likely melatonin is excreted in breast milk
- **Smoking** – not recommended as it may make melatonin less effective
- **Alcohol** – not recommended as it may make melatonin less effective
- **Interactions** – please ensure screening for drug-drug interactions

Side effects

The details below are not a complete list and the BNF and the SPC remain authoritative. Headache, hyperactivity, dizziness, nausea and abdominal pain are the most commonly reported side effects.

Melatonin may affect the reproductive system by inhibiting the hypothalamic-pituitary-gonadal axis.

Monitoring

Consultant:
- Monitor growth in children: annual height and weight
- Review after 2 weeks, then monthly, until optimum dose established.
- Sleep diary.

Review continued need every 6-12 months (dose reduction and /or trial stop).

GP:
- Compliance
- Side effects
- Symptom control

Report any serious adverse reaction to the MHRA, using the yellow card system.

Interactions

The details below are not a complete list and the current BNF and the SPC remain authoritative.

- Fluvoxamine, cimetidine, oestrogens, quinolones and 5- or 8-methoxypsoralens may increase melatonin levels by inhibiting its metabolism.
- Smoking, carbamazepine and rifampicin may decrease melatonin levels due to induction of CYP1A2.
- Alcohol reduces melatonin effectiveness.
- Enhancement of sedative effects of benzodiazepines and z-drug hypnotics.

The specialist will be responsible for checking interactions when melatonin is initiated.

The GP should contact the specialist for advice if the patient is started on any of these medications by other prescribers.

Re-Referral guidelines

Patients who are being treated on the advice of the secondary care team, but are no longer being seen in that setting, may still need review should problems arise. The appropriate level of care and/or advice should be available from the secondary care team in a timely manner without requiring a new referral. Include route of return' should their condition change (such as a return of symptoms, or a development of adverse effects)

Ordering information N/A

Contacts for Support, education and information

Office Hours – Specialist DBH FT Paediatric Dept Tel: 01302 366666

Out of hours – On-call Paediatrician DBHFT Tel: 01302 366666

RDASH FT CAMHS Dept Tel: 01302 796191

ADHD Clinic – Address: Jubilee 2, Tickhill Road Site. (01302) 796880, 789149

It will be presumed by the referring specialist that the primary care team is operating under this shared care guideline. Should the primary care prescriber feel unable to act under this shared care guideline they should discuss with the specialist requesting the care in the first instance. If after discussion they still feel unable to prescribe then the primary care clinician must notify the specialist in writing.

This is guidance on the management of a condition not a commissioning arrangement

References

Full list of side-effects is given in the Circadin summary of product characteristics (SPC), available from www.emc.medicines.org.uk .

https://www.england.nhs.uk/wp-content/uploads/2018/03/responsibility-prescribing-between-primary-secondary-care-v2.pdf

British National Formulary for Children, available at https://bnfc.nice.org.uk/drugs/melatonin/

Medicines Health Regulatory Authority. Summary Report for Importation of Unlicensed Medicines. May 2009, available at http://www.mhra.gov.uk/home/groups/is-lic/documents/websiteresources/con051815.pdf

National Institute for Health and Care Excellence. ESUOM2: Sleep disorders in children and young people with ADHD: melatonin, available at http://www.nice.org.uk/mpc/evidencesummariesunlicensedofflabelmedicines/ESUOM2.jsp

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Challenging behaviour and learning disabilities: prevention and interventions for people with learning disabilities whose behaviour challenges. Available at https://www.nice.org.uk/guidance/ng11/chapter/Recommendation

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