

Prescribing Guidelines: Melatonin

Scope: Prescribing in the Developmental Neurosciences & Learning Disabilities Directorate and Children's Directorate

KEY POINTS FOR IMPLEMENTATION

- Before starting treatment, traditional non pharmacological sleep hygiene methods must have failed.
- The licensed product melatonin 2 mg MR (Circadin®) is to be used **first line, in an off-label way**, if clinically appropriate.
- If prescribing an unlicensed product, because e.g. the patient is unable to swallow tablets,, Bio-melatonin 3mg is recommended..

Always specify the manufacturers' name on the prescription. This will ensure the patient receives melatonin from a consistent source.

It is clinically appropriate to transfer prescribing of licensed melatonin, even if used off label, or unlicensed Bio- melatonin into primary care, under the guidance of an Essential Shared Care Agreement (ESCA) which is available on the Trust intranet.

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1. PRACTICAL GUIDANCE FOR PRESCRIBING MELATONIN

1. Before starting treatment, traditional non pharmacological sleep hygiene methods must have been tried and failed.
2. The usual starting dose for sleep disorders is 2-3 mg in children above the age of two. The dose may be increased to 4-6 mg if there is insufficient benefit after 1-2 weeks. Doses higher than 10 mg are not considered to be of greater efficacy. If no benefit is seen after 2 weeks, then melatonin should be stopped.
3. A dose of 9 mg immediate release is given before EEG investigations.
4. It is recommended that melatonin be given on an empty stomach, since the absorption may be delayed when taken with large meals. It should be taken 30-60 minutes before bedtime.
5. The aim is to establish healthy sleep habits with the lowest effective dose. At least six months of an improved sleep pattern should elapse before withdrawal takes place. Withdrawal may occur over a period of 3-4 weeks. For some children however withdrawal is not successful and treatment may be necessary long term.
6. It is recommended that the patients are followed up two weeks after initiation and then every six months to ensure continuing benefit of melatonin.
7. The licensed product melatonin 2 mg MR (Circadin®) is to be **used first line**, for an off-label indication, if clinically appropriate. Once stabilised, shared care is appropriate, in accordance with the ESCA. It is worth noting that Circadin is a modified release tablet, which cannot be crushed.
8. If an unlicensed product is clinically indicated, rather than the licensed product, e.g. because of swallowing difficulties, or because of the release characteristics, then Bio-melatonin 3mg is recommended for use wherever possible. .. Once stabilised, shared care is appropriate, in accordance with the ESCA.
9. The off-label or unlicensed use of melatonin should be documented in the patient's clinical notes recording that it has been discussed with the patient and / or the carers and parents, and the Trust leaflet supplied. The Trust has also its own Patient Information Leaflet on Melatonin.
10. To ensure that the MHRA guidance is adhered to, the safe prescribing of melatonin in children and adults will be audited every six months.

2. BACKGROUND

Melatonin, the hormone of the pineal gland, is normally made in response to dropping light levels at night and after morning exposure to daylight. When given to humans it has a rapid half-life of half to one hour, producing transient, mild sleep inducing effects. (1) It lowers alertness, body temperature and performance during the three or four hours after a low dose has been given. Correctly timed, it is able to shift the internal 'body clock' both to later and earlier times. (2)

3. EFFICACY

There is one systematic review, two meta-analysis and many published randomised controlled trials which assess the safety and efficacy of melatonin in children and adolescents. (3) Few studies have been published reporting the contrary (possibly because of reporting bias). However there have been very few well designed controlled and long term studies. Clinical experience suggests that melatonin can induce and maintain sleep. (1)

4. INDICATIONS

Melatonin is indicated for treating sleep disorders in children and adults with neurodevelopment disorders and conditions such as visual impairment, cerebral palsy, attention deficit hyperactivity disorder and autism. It is also sometimes used before EEG investigations.

Following a comprehensive review of the literature by the Medicines Management Committee, the Trust recommended that there was insufficient published clinical and economic evidence to support the routine use of melatonin (Circadin®) as monotherapy for the short-term treatment of primary insomnia in patients who are aged 55 or over (it's licensed indication).

5. DOSE

Before starting treatment, traditional non pharmacological sleep hygiene methods must have been tried and failed. In exceptional circumstances e.g. West Syndrome and Tuberous Sclerosis, treatment may be started immediately.

The usual starting dose for sleep disorders is 2-3 mg in children above the age of two. The dose may be increased to 4-6 mg if there is insufficient benefit after 1-2 weeks. The maximum dose is generally accepted to be 10 mg. (4) Doses higher than 10 mg are not considered to be of greater efficacy and may cause increased side-effects. If no benefit is seen after 2 weeks on the higher dose then melatonin should be stopped.

Immediate release formulations may be more effective in inducing sleep, sustained release formulations may be better for maintenance of sleep. (5)

A dose of 9 mg immediate release should be given before EEG investigations.(4)

6. ADMINISTRATION

It is recommended that melatonin be given on an empty stomach, since the absorption may be delayed when taken with large meals. It should be taken 30-60 minutes before bedtime. (4)

Powder from the capsules may be dispersed in water, milk or orange juice. The powder may also be mixed with water and flushed down a PEG or NG tube. (5)

7. ADVERSE EFFECTS

In clinical studies the most common adverse events were headache, pharyngitis, back pain and asthenia. These occurred at a similar frequency to placebo. (6)

There was no evidence of withdrawal effects following treatment discontinuation. (6) Vivid dreams and nightmares have been reported. (7)

Some reports suggest melatonin improves seizure control when used in patients with epilepsy; others indicate that it may worsen seizure control. When used in patients with epilepsy, it is important to closely monitor the effect of melatonin on seizure frequency. (8) No robust large controlled clinical studies have been conducted in children and adults with LD and epilepsy taking melatonin, so its safety in this group has not been established.

8. DURATION OF TREATMENT

The duration of treatment is variable.

The aim is to establish healthy sleep habits with the lowest effective dose of melatonin. It is suggested that at least six months of an improved sleep pattern should elapse before withdrawal takes place. Withdrawal may occur over a period of 3-4 weeks and change in sleep pattern observed. For some children however withdrawal is not successful and treatment may be necessary long term.

Tolerance is characterised by the administration of a drug in higher doses to achieve the same effect. It is not listed on the Summary of Product Characteristics (SPC) for Circadin®. However, some clinical experience from the National Child and Adolescent Learning Disability Psychiatry Network suggests that the efficacy may be lost if melatonin is prescribed for longer than two years. It suggests that if the melatonin is withdrawn prior to this, sensitivity may be re-established and melatonin successfully re-introduced at a lower dose. (7) Patients should be followed up every six months to ensure continuing benefit of melatonin. Standard monitoring of growth and sexual development is recommended i.e. to check height, weight and pubertal development progress as expected.

9. CLINICAL GOVERNANCE

In August 2008 the MHRA issued guidance on the use of melatonin. (9) Many non-pharmaceutical grade products of melatonin are being imported from countries where melatonin products are classed as food supplements, not medicines, they are not required to be manufactured to the standard of Good Manufacturing Practice (GMP) normal for pharmaceuticals. It is believed that at least 50 melatonin preparations are being imported into, or manufactured in the

UK. To encourage the use of melatonin manufactured according to GMP the MHRA advised that if imported melatonin was used then the special clinical need should be provided to the importer for submission to the MHRA.

Melatonin 2 mg prolonged release (Circadin®) is now licensed as monotherapy for the short term treatment of primary insomnia in adults aged 55 years and over. The MHRA advised ... **'It is therefore important to ensure that the licensed product available in the UK is used where possible.'**

If this dosage or formulation of Circadin® is not appropriate a melatonin product manufactured according to GMP (preferably Bio-Melatonin 3mg tablets) should be used, although this will be an unlicensed product. In both cases there should be an explanation to parents/carers as to the off-label or off licence use of melatonin. Appropriate consent should be obtained and filed in the patient's notes. Patient information leaflets are available on the Trust intranet to explain the use of unlicensed medication.

10. PREFERRED SUPPLIERS

In accordance with the MHRA advice the following is recommended within the trust:

1. First line -The licensed product melatonin 2 mg MR (Circadin®) for an unlicensed indication, if the dose is appropriate.
Second line - Melatonin manufactured in the UK according to GMP (preferably Bio-Melatonin 3mg tablets). NB The manufacturer provides the following information: *The tablet may be crushed if required for easier swallowing. Stability data demonstrates the tablet may be crushed and dissolved in up to 200mls of water. The dissolved tablet may be flushed through a percutaneous endoscopic gastrostomy (PEG) tube or nasogastric (NG) tube..*

11. REFERENCES

- 1 Wassmer E and Whitehouse WP. Melatonin and sleep in children with neurodevelopmental disabilities and sleep disorders. *Current Paediatrics*;2006;16:132-8
- 2 Arendt J. Melatonin. *British Medical Journal* 1996;312:1242-3
- 3 Melatonin in paediatric sleep disorders. London New Drugs Group September 2008
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- 6 Regional Drug and Therapeutics Centre. Melatonin for sleep disorders in adults. *New Drug Evaluation No. 90* June 2008
- 7 National Children and Adolescent Learning Disability Psychiatry Network. 2008
- 8 Alder Hey Royal Liverpool Children's NHS Trust. Guidelines on melatonin. 2000
- 9 Drug Procurement Advise. Restrictions on the import of unlicensed melatonin products following the grant of a marketing authorisation for Circadin® 2mg tablets. MHRA August 2008