

## Prescribing Support Information

### MELATONIN prolonged release tablets (Slenyto® and Circadin®) for the treatment of persistent chronic sleep disorders in adults and children

#### AMBER following specialist initiation

**Scope:** This information is used to support prescribers in managing patients who have been initiated on melatonin (Slenyto® and Circadin®) by a specialist for the management of persistent chronic sleep disorder. This document does not include other forms of licensed melatonin such as melatonin 2mg capsules (Colonis®), melatonin 3mg tablets (Colonis®) or melatonin 1mg/ml liquid (Colonis) which are licensed for short term use in jet lag. The melatonin 1mg/ml liquid has been assessed and the quantities of polyethylene glycol may be excessive for some children. Other unlicensed melatonin preparations or melatonin food supplements remain RED due to the variation in quality, cost to primary care and lack of evidence regarding suitability of excipients in children. **For certain patients, unlicensed melatonin may be required ie patients with feeding tubes. In this circumstance prescribing, monitoring and review responsibilities will be held by specialist.**

Your patient has been identified as being suitable to receive melatonin in accordance with the indications detailed below. They have been started on treatment and have been reviewed to assess the efficacy and adverse effects of the treatment by the specialist team.

Melatonin has been considered as appropriate for prescribing in primary care and the information contained in this document has been provided to support you to prescribe the medicine for your patient in the community. Your patient's dose is now stable and is detailed in the clinic letter.

#### **Background**

Paediatric insomnia is a widespread problem, with an overall prevalence of 1% to 6%, but rising to 50% to 75% in children with NDD (neurodevelopmental disorders) or psychiatric comorbidities, and specifically Autistic Spectrum Disorder (ASD and NDD) [1]. Sleep problems often carry on into adulthood. These sleep disturbances exacerbate both cognitive performance deficits and behavioural problems which compound entire-family distress [1].

In adults sleep studies have shown varied results as to the prevalence of insomnia. Some estimates show that about 10% - 30% of adults complain of chronic insomnia. This increases across different demographic populations due to co-morbidities or use of medication [2].

Current practice recommends behavioural sleep interventions (sleep hygiene) as first-line management for insomnia. Pharmacotherapy is often considered when behavioural intervention is insufficient [1].

#### **Melatonin**

Melatonin is a hormone secreted by the pineal gland in response to decreased light, mediated through the suprachiasmatic nucleus. The mechanism of action of melatonin is to supplement the endogenous pineal hormone [3].

#### **Available formulations**

##### **Melatonin 1mg & 5mg prolonged release minitabs (Slenyto®)**

- For children aged 2 years and above
- Patient with ASD or SMS. **Slenyto® should only be used in these indications, or for patients unable to swallow Circadin® with persistent chronic sleep disorder associated with conditions specified below (off label).**
- 2-10mg once at night 30-60 mins before bed with food [3]. Off label doses of up to 12mg have been used.

Please note: Slenyto is off label in patients aged 18 years or above. Patients should be maintained on the same formulation if ongoing pharmacotherapy is required into adulthood.

**Melatonin 2mg prolonged release tablets (Circadin ®)**

- For children aged 2 years and above who are able to swallow tablets (off label) and for adults
- Patient with:
  - Attention Deficit Hyperactivity Disorder (ADHD)
  - Cerebral Palsy
  - Chronic fatigue syndrome (CFS)/ myalgic encephalomyelitis (ME) (or encephalopathy)
  - Complex neurodevelopmental disorders (i.e., Angelman’s syndrome, Rett’s syndrome, tuberous sclerosis complex, fragile X syndrome, foetal alcohol spectrum disorder (FASD))
  - Global developmental delay / learning disability
  - Parkinson’s disease with REM sleep disorder.
- 2-10mg 30-60 mins before bed with food [4]. Off label doses of up to 12mg have been used.

**Behavioral Sleep Intervention (Pending local implementation)**

Sleep hygiene must be optimized prior to consideration of melatonin. This is best carried out by someone trained as a sleep practitioner and as part of a structured programme for the family. In certain family or social circumstances i.e. parental ill health, it may not be possible for families to implement behavioral interventions fully to resolve sleep issues. It may be appropriate in these circumstances to commence melatonin to support behavioral interventions. Social support should also be considered. Where the sleep deprivation is severe, it may also be appropriate to commence melatonin to support behavioral interventions. A General Practitioner or specialist should make a clinical judgement around the appropriateness of behavioral sleep intervention.

**Assessment (Specialist to complete)**

- Medical history to be taken
- Sleep history to be taken/reviewed
- Rule out medical causes of insomnia i.e. obstructive sleep apnoea, restless legs syndrome, urticaria, pain etc.
- Prescribe if appropriate

**Initiation & titration [2] (Specialist to complete)**

If behavioral sleep intervention is insufficient or inappropriate at this time, melatonin should be considered if the patient experiences

- <6 hours of continuous sleep persistently for at least 3 months AND/OR
- >0.5 hour sleep latency on at least 3 out of 5 work/school nights per week for 2 weeks.

Starting doses and titration are suggested as follows:

	Slenyto	Circadin
<b>Starting dose</b>	2mg	2mg
<b>Dose increment 1 (after a minimum of 4 weeks)</b>	5mg	6mg <sup>1</sup>
<b>Dose increment 2 (after a minimum of 4 weeks)</b>	10mg	10mg <sup>1</sup>

1. Clinical judgement to be used if smaller dose increments more suitable

Improvements appear within the first week of treatment, which become significant at or by 3 weeks of treatment. Dose increases should be considered after 4weeks if sleep continues to be a problem as defined by:

- <6 hours of continuous sleep (longest sleep episode)
- >0.5 hour sleep latency on at least 3 out of 5 work/school nights per week

Clinical criteria should also be taken into account for daytime repercussions (fatigue, irritability, attention deficits, challenging (externalising) behaviours and well-being (quality of life)). Sleep hygiene should always be optimised prior to consideration of melatonin or further dose increases.

After at least 3 months of treatment, the specialist will evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. The patient should be advised to take a drug holiday prior to this review. This can provide evidence of clinical benefit before ongoing need is established

**Transfer of prescribing into primary care**

Prescribing to be continued by the specialist until

- Follow up review at 3 months
- Evidence of clinical benefit
- Stabilisation of the dose is achieved
- Ongoing need has been established (drug holiday prior to review will support this)

**Drug holidays**

To ascertain ongoing need for melatonin a ‘drug holiday’ should be considered 3 months post initiation and 6 monthly thereafter. Treatment can be stopped abruptly and should be stopped for 2 weeks. A long-term follow-up study showed that discontinuation was not associated with withdrawal effects or rebound insomnia [4]. If sleep improvements are maintained without melatonin, therapy can be stopped. If sleep deteriorates and continues to be an issue, the original dose where sleep improved can be re-instated. Ongoing drug holidays can be considered at review. If there is a consistent correlation of sleep deterioration at drug holiday, patients should be advised to continue without break unless they are suspected to be a poor metaboliser of melatonin.

Poor metabolisers of melatonin may find that melatonin efficacy reduces over time. In these patients, melatonin accumulates in the plasma. This leads to an absent peak concentration at bedtime. This is identified through clinical history; patients may report initial benefit with melatonin and then ineffectiveness. These patients may need regular 2-week washout periods if benefit wanes to see continued effect with melatonin. A drug holiday when effect has waned will facilitate washout and patients often see benefit after recommencement. Patients should be counselled regarding this on initiation by the specialist.

**Ongoing Review**

Monitor sleep and suitability to continue melatonin every 12 months. Review longest sleep episode and sleep latency. See ‘initiation & titration’ for suggested criteria for increasing melatonin therapy.

No blood monitoring is required. General observation of these children is recommended. A study by Malow et al showed that long term melatonin therapy continues to be effective and has shown that there are no significant effects on growth or pubertal development [4]. This has also been corroborated by Van Geijlswijk et al [5] in an earlier study. These studies followed up children after 2 and 3.1 years of melatonin therapy respectively.

**How long the medicine should be prescribed for**

The duration of treatment benefit may vary between individuals. Treatment with melatonin should be continued only when considered to be beneficial. If the patient appears to be gaining no benefit from melatonin, treatment should be stopped. Information from drug holidays should be considered as this allows comparison and highlights impact of melatonin pharmacotherapy.

**Responsibilities**

<b><u>Specialist service</u></b>	<b><u>Primary Care</u></b>	<b><u>Patient</u></b>
Initial assessment	Ongoing review	6 monthly drug holidays
Review until stable	Ongoing prescribing	Annual Sleep diary once stable on and off medication (1 week duration for each)
Prescribe until stable		
Transfer to primary care after stable		

**Administration (see patient information leaflet )**

Slenyto® minitabs should be swallowed whole to maintain the prolonged release properties of the formulation. Tablets can be put into food such as yoghurt, orange juice or ice-cream to facilitate swallowing and improve compliance. If the tablets are mixed with food or drink, they should be taken immediately, and the mixture not stored [6].

Circadin should be swallowed whole to maintain the prolonged release properties of the formulation [7].

**Patient information leaflets**

[Medicines for children](#)

[Circadin®](#)

[Slenyto®](#)

**Special warnings/cautions [6,7]****Drowsiness**

Melatonin may cause drowsiness. Therefore, the medicinal product should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety. Note that this may be more likely to occur in patients who are CYP1A2 poor metabolisers [4].

**Autoimmune diseases**

No clinical data exist concerning the use of melatonin in individuals with autoimmune diseases. Therefore, melatonin is not recommended for use in patients with autoimmune diseases.

**Renal impairment**

The effect of any stage of renal impairment on melatonin pharmacokinetics has not been studied. Caution should be used when melatonin is administered to such patients [3,4].

**Hepatic impairment**

There is no experience of the use of melatonin in patients with liver impairment. Published data demonstrates markedly elevated endogenous melatonin levels during daytime hours due to decreased clearance in patients with hepatic impairment. Therefore, melatonin is not recommended for use in patients with hepatic impairment [3,4].

**Contra-indications [6,7]**

Hypersensitivity to the active substance or to any of the excipients.

**Lactose:** Slenyto® and Circadin® contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take these medicines.

**Interactions with other medicines [6,7]**

Interaction studies have only been performed in adults. In the absence of specific studies in children, the drug interactions with melatonin are those known in adults. Melatonin is known to interact with; **fluvoxamine, benzodiazepines, non-benzodiazepine hypnotics, thioridazine, imipramine, alcohol, 5- or 8-methoxypsoralen, cimetidine, oestrogens, CYP 1A2 inhibitors or inducers, smoking, NSAIDs, beta blockers.**

**Adverse effects [6,7]**

The most frequently reported adverse reactions with Slenyto® in clinical studies were somnolence, fatigue, mood swings, headache, irritability, aggression, and hangover occurring in 1:100-1:10 children. The following adverse reactions (frequency unknown) have been reported with Circadin®: epilepsy, visual impairment, dyspnoea, epistaxis, constipation, decreased appetite, swelling face, skin lesion, feeling abnormal, abnormal behaviour and neutropenia.

**References**

1. Gringras,P. et al. Efficacy and Safety of Paediatric Prolonged –Release Melatonin for Insomnia in Children with Autism Spectrum Disorder. J Am Acad Child Adolesc Psychiatry. 2017;56(11):948- 95
2. Bhaskar, S et al. Prevalence of chronic insomnia in adult patients and its correlation with medical comorbidities. Journal of Family Medicine and Primary Care. 2016; 5(4), 780-784.
3. Wurtman,R. Physiology and available preparations of melatonin. [https://www.uptodate.com/contents/physiology-and-available-preparations-of-melatonin?search=melatonin&source=search\\_result&selectedTitle=1~110&usage\\_type=default&display\\_rank=1](https://www.uptodate.com/contents/physiology-and-available-preparations-of-melatonin?search=melatonin&source=search_result&selectedTitle=1~110&usage_type=default&display_rank=1) (accessed 29/8/19).

4. Malow et al. Sleep, Growth, and Puberty After Two Years of Prolonged-Release Melatonin in. *Journal of the American Academy of Child & Adolescent*. 2020.
5. Van Geijlswijk IM, Mol RH, Egberts TC et al. Evaluation of sleep, puberty and mental health in children with long-term melatonin treatment for chronic idiopathic childhood sleep onset insomnia. *Psychopharmacology (Berl)* 2011; 216:111.
6. Flynn Pharma. *Slenyto 1 mg prolonged-release tablets*. <https://www.medicines.org.uk/emc/product/10023/smpc> (accessed 23/12/19).
7. Flynn Pharma. *Circadin 2 mg Prolonged-release Tablets*. <https://www.medicines.org.uk/emc/product/2809> (accessed 23/08/19).