PrescQIPP
Community Interest Company

# Melatonin

The annual spend in England and Wales on all melatonin preparations (ePACT2 Feb-Apr 19) is £30 million; £7.8 million of this is for unlicensed melatonin preparations. The first paediatric licensed melatonin preparations (Slenyto® 1mg and 5mg tablets) and the first melatonin preparations licensed for the short-term treatment of jet lag in adults (melatonin 3mg tablets, melatonin 1mg/ml oral solution) are now available.[1,2,3] These new melatonin preparations are reviewed and consideration given to their use in preference to unlicensed melatonin preparations. There may be significant cost pressures if they are introduced without consideration given to medicines optimisation.

Medicine optimisation projects in this area include reviewing the evidence base for unlicensed uses, melatonin treatment reviews, licensing considerations, and product selection and dose optimisation to avoid increased costs.

## Recommendations

- Ensure that children have undergone a trial of parent-directed behavioural sleep interventions before considering prescribing melatonin within licensed indications.[1]
- Melatonin 1mg/ml oral solution (Colonis Pharma Ltd) should not be used in children and adolescents due to safety and efficacy concerns.[3]
- Do not prescribe melatonin for sleep disorders associated with Attention Deficit Hyperactivity Disorder (ADHD) without a concomitant disorder of Autistic Spectrum Disorder (ASD) or for shift work.
- Do not prescribe melatonin for jet lag on NHS prescription as GPs are not responsible for providing NHS prescriptions for conditions which may arise while abroad or travelling.[4] If wanted, GPs may provide private prescriptions for melatonin in anticipation of jet lag.
- Be aware that the risks associated with the long-term use of benzodiazepine and 'Z-drug hypnotics have been well recognised for many years. Recent data also suggest a similar safety concern with melatonin. These risks include falls, accidents, cognitive impairment, dependence and withdrawal symptoms, and an increased risk of dementia.[5]
- Be aware that little is known about the long-term effects of melatonin (data is available for up to six months in adults and two years in children).[1,2,3,6]
- Review the continued need for and effectiveness of melatonin in children after the first three months, then at six monthly intervals for up to two years treatment (data is available for up to two years treatment).[1]
- Consider a trial withdrawal of treatment after two years melatonin treatment in children as efficacy and safety data are not available beyond two years treatment; in adults review melatonin and consider a trial withdrawal or stopping treatment after thirteen weeks.[1,6]
- Do not add melatonin to the repeat prescription list as use should be short-term.[1,2,3,6] If needed, only allow up to two repeat prescriptions of four weeks duration maximum.
- Patients with swallowing difficulties should be prescribed the following licensed melatonin preparations off-label, in preference to using an unlicensed melatonin preparation.[7]
  - » **For an immediate release dose**: Halve, quarter or crush Circadin® P/R 2mg tablets, Slenyto® P/R 1mg or 5mg tablets, melatonin 3mg tablets or use melatonin 1mg/ml oral solution (Colonis Pharma Ltd).

## Recommendations

  - **For a prolonged-release melatonin dose**: mix whole Slenyto® P/R 1mg or 5mg tablets with yoghurt, orange juice or ice cream and take immediately to aid swallowing. Do not break, crush or chew them. If this is not suitable, then change to an immediate release melatonin preparation as above.
- Melatonin 1mg/ml oral solution (Colonis Pharma Ltd) contains the following excipients which may be potentially problematic when used in children:[3,8]
  - Propylene glycol 150.37 mg per 1ml dose
  - Sorbitol 140 mg per 1ml dose
- The total daily dose of excipients needs to be calculated and checked whether they are within the safety limits for the age and weight if melatonin 1mg/ml oral solution (Colonis Pharma Ltd) is being considered for use in a child.[8]
- Review patients prescribed unlicensed melatonin preparations for the continued need for melatonin, any adverse effects and then for suitability for a switch to a licensed or off-label use, melatonin preparation.
- Follow General Medical Council (GMC) guidance when prescribing an unlicensed medicine, prescribers must be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy. An unlicensed medicine may be prescribed when there is no suitably licensed medicine that meets the patient's need.[9]
- Optimise melatonin doses so that use is within licensed doses and also to manage additional cost pressures.
- If a lower treatment effect is seen with Slenyto® after titration to a higher dose of melatonin, first consider a down-titration to a lower dose before deciding on a complete discontinuation of treatment. For example, patients recently increased to 5mg should be lowered back to 2mg and patients recently increased to 10mg should be lowered back to 5mg.[1]
- Monitor children for a possible impact of melatonin on their pubertal development.[10,11]

## Background

Melatonin is a naturally occurring hormone produced by the pineal gland in the brain. It is involved in coordinating the body's sleep-wake cycle and helping to regulate sleep.[11]

A licensed melatonin preparation for use in adults 55 years or over has been available for some time.[6] Circadin® (melatonin) prolonged-release (P/R) 2mg tablets are licensed in patients who are aged 55 or over for the short-term treatment of primary insomnia characterised by poor quality of sleep. The dose may be continued for up to 13 weeks.[6]

The following melatonin preparations have recently been licensed:

- Slenyto® (melatonin) 1mg and 5mg prolonged release tablets[1]
- Melatonin 3mg tablets (Colonis Pharma Ltd)[2]
- Melatonin 1mg/ml oral solution (Colonis Pharma Ltd)[3]

Table 1 on the next page compares their licensed indications and licensed age groups and includes Circadin® prolonged release tablets for comparison.

**Table 1: Comparison of licensed uses of melatonin preparations**[1,2,3,6]

| Product | Licensed indication | Age licensed for | Dose, treatment duration and review |
|---|---|---|---|
| Slenyto® 1mg and 5mg prolonged release tablets | Treatment of insomnia in children and adolescents aged two to 18 years with ASD and/or Smith-Magenis Syndrome (SMS) where sleep hygiene measures have been insufficient | Age two to 18 years | 2mg nightly increased to 5mg if needed<br>Maximum 10mg<br>Review at three months then six monthly<br>Up to two years duration |
| Melatonin 3mg tablets (Colonis Pharma Ltd) | Short-term treatment of jet lag in adults | Adults (18 years and over) | 3mg daily for maximum five days<br>Dose can be increased to 6mg daily<br>Maximum five day course and 16 courses per year<br>Do not prescribe on NHS prescription for jet lag |
| Melatonin 1mg/ml oral solution (Colonis Pharma Ltd) | Short-term treatment of jet lag in adults | Adults (18 years and over) | 3mg daily for maximum five days<br>Dose can be increased to 6mg daily<br>Maximum five day course and 16 courses per year<br>Do not prescribe on NHS prescription for jet lag |
| Circadin® 2mg prolonged release tablets | Short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over | Adults aged 55 years and over | 2mg nightly for up to 13 weeks |

The first melatonin preparation licensed for use in children, Slenyto®, is now available.[1,11] Around 60% of melatonin prescriptions are for use in children (Jan-Dec 18 ePACT2). The prevalence of sleep disturbance in children and adolescents with ASD ranges from 30%–53% and up to 70% in those with ADHD. If untreated, such sleep disturbances can negatively impact children, adolescents, and their families with respect to physical and mental health, social, academic, and cognitive functioning.[12]

Slenyto® 1mg and 5mg P/R tablets are licensed for the treatment of insomnia in children and adolescents aged two to 18 years with ASD and/or Smith-Magenis Syndrome (SMS) where sleep hygiene measures have been insufficient.[1] Slenyto® is not licensed for use in children with ADHD without a concomitant disorder of ASD.

The recommended starting dose is 2mg. If needed, the dose is increased to 5mg, up to a maximal dose of 10mg. The dose is taken once daily, ½ -1 hour before bedtime and with or after food. Up to two years treatment is included in the product licence with a review in the first three months and then every six months. After at least three months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen.[1] The adult dose is lower than the children's dose as it is known that the metabolism of melatonin declines with age.[6]

Slenyto® P/R tablets and Circadin® P/R tablets are produced by the same manufacturer, Flynn Pharma Ltd.[1,6] Slenyto® P/R tablets were developed to have a similar pharmacokinetic profile as Circadin® P/R tablets but presented in a smaller tablet (3mm) suitable for paediatric use.[11] They are film-coated tablets and cannot be broken, crushed or chewed because the prolonged release properties would be lost. Although the tablets should be swallowed whole, they can be put into food such as yoghurt, orange juice or ice-cream to aid swallowing and improve compliance. If mixed with food or drink, the tablets should be taken immediately.[1]

A new melatonin 3mg film-coated tablet and melatonin 1mg/ml oral solution (Colonis Pharma Ltd) are now licensed for the short-term treatment of jet lag in adults. The standard dose is 3mg daily for a maximum of five days. The dose may be increased to 6mg if the standard dose does not adequately alleviate symptoms. The dose that adequately alleviates symptoms should be taken for the shortest period.[2,3] They are prescription only medicines (POMs) and so cannot be purchased over the counter (OTC).[2,3] They should not be prescribed on the NHS for jet lag.

Melatonin used for jet lag would be classified as a medicine used for travel and in anticipation of an ailment. GPs are not responsible for providing NHS prescriptions for conditions which may arise while abroad or travelling. The General Medical Services Regulations 2015 state that GPs may demand or accept (directly or indirectly), a fee or other remuneration for prescribing or providing drugs, medicines or appliances (including a collection of such drugs, medicines or appliances in the form of a travel kit) which a patient requires to have in their possession solely in anticipation of the onset of an ailment or occurrence of an injury while that patient is outside of the United Kingdom but for which that patient is not requiring treatment when the drug, medicine or appliance is prescribed.[4] GPs may issue private prescriptions for their patients for melatonin 3mg tablets or melatonin 1mg/ml oral solution (Colonis Pharma Ltd) if used in anticipation of jet lag.

Some savings may be made by switching from unlicensed melatonin preparations to licensed products Circadin®, Slenyto®, melatonin 3mg tablets (Colonis Pharma Ltd) or melatonin 1mg/ml oral solution (Colonis Pharma Ltd). Conversely, there will be significant additional costs for some switches from unlicensed to licensed melatonin preparations. Consideration needs to be given to these potential cost pressures when considering switching preparations.

# Evidence base

## Melatonin licensed uses

In the clinical trials supporting the licence application for melatonin use in adults, Circadin® 2mg each evening was more effective than placebo at improving the quality of sleep and the patient's ability to function normally on the following day over a three week treatment period.[6] The combined results showed that 32% of patients taking Circadin® (86 out of 265) reported a significant improvement in symptoms after three weeks, compared with 19% of those taking placebo (51 out of 272).[13] An additional study supporting the licence for up to 13 weeks treatment demonstrated improvements in sleep latency, quality of sleep and morning alertness, with no withdrawal symptoms and rebound insomnia. The study showed that the benefit observed after three weeks is maintained for up to three months but failed the primary analysis set at six months. Quality of life was improved significantly with Circadin® 2mg compared to placebo in one of the studies.[6]

The Midlands Therapeutic Review and Advisory Committee (MTRAC) summarised the evidence for efficacy of prolonged release (PR) melatonin for treatment of primary insomnia in adults in October 2013.[14] The evidence was based on three randomised, placebo-controlled trials with highly subjective outcomes. Two of the trials showed that P/R melatonin shortened sleep latency times by nine and 15 minutes respectively compared to placebo. None of the trials showed a significant effect on total sleep time. There were no comparisons with other treatments for insomnia. MTRAC gave P/R melatonin a low place in therapy.

A National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summary (CKS) reviewed the evidence for melatonin use for long-term (>four weeks) insomnia from age 16 years onwards.[15] The CKS suggests there is some evidence to suggest that melatonin may improve some sleep-related parameters in older people with insomnia. Three randomised controlled trials demonstrated an improvement in quality of sleep and morning alertness with melatonin 2mg PR daily, although the clinical significance of the improvement is unclear. In two of the studies, a small improvement in sleep-onset latency (the time taken to get to sleep) was also noted with melatonin. CKS identified no studies comparing PR melatonin with hypnotics for the treatment of insomnia.

The pivotal trial used for the licence application for Slenyto® was conducted in 125 children with ASD or SMS and sleep disturbances despite sleep hygiene and behavioural interventions.[16] Children were aged 2-17 years (mean age 8.7 years +/- 4.15 years). The trial consisted of a 13- week randomised placebo-controlled trial (RCT) followed by a 91-week open-label study. Seventy-two children completed the full study. At 52 weeks the following melatonin P/R doses were used in the evening: 2mg (22%); 5mg (36%) 10mg (42%). The average daily dose was 5.3mg. Only four children with SMS were included, the remainder had ASD. 28.8% children also had a concomitant diagnosis of ADHD. Over half the children (65.6%) had taken melatonin prior to study entry, mostly immediate release melatonin (88%) and some controlled release (6%).[11]

In the 13-week RCT, Total Sleep Time (TST) improved by 32.43 minutes (p=0.034) and sleep latency (SL-time until falling asleep in evening) improved by 25.30 minutes (p=0.011) with melatonin compared to the placebo group. There was improvement in the duration of uninterrupted sleep, but this did not reach statistical significance at 13 weeks. Although, Slenyto® did induce positive effects on both sleep latency and total sleep time, it did not significantly improve the number of awakenings per night, wake time after sleep onset, composite sleep disturbance index and overall daytime behaviour. Caregivers daytime sleepiness or quality of sleep at night showed no statistically significant differences.[11] Treatment effects on child behaviour and caregivers quality of life were evaluated. Melatonin treatment resulted in significant improvement in externalizing but not internalising behaviour (Strengths and Difficulties questionnaire; SDQ) compared to placebo (p = 0.021) with clinically relevant improvements in 53.7% of melatonin treated versus 27.6% of placebo treated children (p = 0.008). Caregivers quality of life also improved with melatonin versus placebo (p = 0.010) and correlated with the change in total SDQ (p = 0.0005). Melatonin alleviated insomnia-related difficulties, particularly externalising behaviour in the children, subsequently improving caregivers quality of life.[17]

The trial outcomes are not fully in line with the European Medicines Agency (EMA) insomnia guidelines which state that effects on sleep latency or maintenance of sleep should be supported by improvement in quality of day-time function. The improved well-being of the parents/caregivers seen in the trial was viewed as offering some support for the beneficial effects in children given that the impact of the childrens disturbed sleep directly impacts the parents/caregivers.[11]

The improvements in TST, SL and duration of uninterrupted sleep seen in the double blind-phase of the trial were maintained throughout the open-label follow up period. Discontinuation rates were generally low with more patients discontinuing in the placebo group compared to the melatonin P/R group.[11]

Around 37% of children dose-escalated to the 10mg dose did not receive benefit from the dose. Prescribers should consider a down-titration from a higher dose before discontinuing treatment due to lack of efficacy, in case the effect is lower at this dose than at the next lower dose. Some individuals are slow CYP 1A2 metabolisers and may get extensively high melatonin levels if treated at higher doses.[11]

## Jet lag

A melatonin 3mg film-coated tablet and melatonin 1mg/ml oral solution (Colonis Pharma Ltd) are now licensed for the short-term treatment of jet lag in adults. The standard dose is 3mg daily for a maximum of five days. The dose may be increased to 6mg if the standard dose does not adequately alleviate symptoms. The dose that adequately alleviates symptoms should be taken for the shortest period. There is a maximum of five days treatment per course and 16 courses per year included in the license.[2,3]

The NHS website advises that medicines are not usually needed for jet lag. Symptoms often improve after a few days as the body clock adjusts to the new time zone. Sleeping tablets may be helpful for insomnia, but they can be addictive so should only be used for a short time and if symptoms are severe. Melatonin supplements are not recommended for jet lag because there is not enough evidence to show they work.[18]

The CKS on the management of jet lag does not recommend the use of melatonin as there is limited and conflicting evidence of benefit.[19]

- A Cochrane systematic review of nine randomised trials assessed the effects of melatonin on various subjective jet lag symptoms compared with placebo. In eight trials melatonin reduced subjective ratings of symptoms such as fatigue compared with placebo, if taken close to the target bedtime at the destination. It suggested that the benefit is likely to be greater the more time zones are crossed and for eastwards travel. It suggested the short-term occasional use of melatonin for the prevention and treatment of jet lag, however it highlighted the need for the correct timing of the medication, as if taken early in the day, it may cause sleepiness and delay adaptation to the new time zone, and it had an uncertain adverse effect profile. The Cochrane review recommends melatonin for adult travellers flying across five or more time zones, particularly in an easterly direction, and if they have experienced jet lag on previous journeys. They do note that no differences were detected between daily doses of 0.5 and 5mg melatonin, except that people fell asleep faster and slept better after 5mg than 0.5mg. For many people 5mg may be a higher dose than necessary: 2 or 3mg may therefore be preferable to start. In one study a 2mg slow-release melatonin was shown to be ineffective, suggesting that a pulse of melatonin, briefly giving a higher concentration in the blood, works better.[20]
- An American Academy of Sleep Medicine (AASM) report states that melatonin given following travel improves the duration and quality of sleep based on both subjective and objective measures, however the most effective dose of melatonin for jet lag disorder is unclear.[21]
- Melatonin has potential hypnotic and phase-shifting effects, however expert opinion in a review article states there are insufficient trial data to recommend its use, with some studies showing improved sleep and alertness, but others finding little effect.[22]
- An additional review article pooled data from six studies which found that melatonin effect sizes in early studies were not replicated in later studies, suggesting that melatonin may be of limited benefit in reducing jet lag symptoms.[23]

Melatonin 3mg film-coated tablets and melatonin 1mg/ml oral solution (Colonis Pharma Ltd) are prescription only medicines (POMs).[2,3] Melatonin used for jet lag would be classified as a medicine used for travel and in anticipation of an ailment. GPs are not responsible for providing NHS prescriptions for conditions which may arise while abroad or traveling. The General Medical services Regulations 2015 state that GPs may demand or accept (directly or indirectly), a fee or other remuneration for prescribing or providing drugs, medicines or appliances (including a collection of such drugs, medicines or appliances in the form of a travel kit) which a patient requires to have in their possession solely in anticipation of the onset of an ailment or occurrence of an injury while that patient is outside of the United Kingdom but for which that patient is not requiring treatment when the drug, medicine or appliance is prescribed.[4] Patients may request private prescriptions from GPs for melatonin 3mg tablets or melatonin 1mg/ml oral solution (Colonis Pharma Ltd) for the short-term treatment of jet lag.

Use of melatonin 3mg tablets and melatonin 1mg/ml oral solution (Colonis Pharma Ltd) in any indication or age group other than for the short-term treatment of jet lag in adults would be an off-label use.

## Melatonin unlicensed uses

In line with GMC guidance, when prescribing an unlicensed medicine, the prescriber must be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy. An unlicensed medicine may be prescribed when there is no suitably licensed medicine that meets the patient's need.[9]

- Patients prescribed melatonin for use in other unlicensed clinical conditions should have their treatment reviewed for effectiveness, adverse effects and alternative options explored.
- Patients commenced on melatonin should have regular treatment reviews scheduled into their clinical notes.

## Sleep disorders in children (other than ASD or SMS)

The main treatments available for children and young people with sleep disorders are non-drug treatments, including good 'sleep hygiene'. Good sleep hygiene includes day-to-day things that can be done at home to help children and young people sleep. This includes advice such as having fixed times for going to bed, avoiding exercise and eating a heavy meal near bedtime, keeping the bedroom comfortable and relaxing near bedtime.[24]

Clinical experience suggests that when appropriate behavioural sleep interventions fail, melatonin may be of value for treating sleep onset insomnia and delayed sleep phase syndrome in children with conditions such as visual impairment, cerebral palsy, attention deficit hyperactivity disorder, and learning difficulties.[10]

NICE published an evidence summary on the use of melatonin in children and young people with ADHD with sleep disorders in January 2013.[24] The key points from the evidence are:

- No high-quality studies were identified that provided evidence for the efficacy of prolonged-release melatonin tablets (licensed in the UK) used off-label in children with sleep disorders and ADHD.
- Limited evidence for unlicensed melatonin products was identified from two small (n=105 and n=19) short term randomised controlled trials (RCTs) and one small, long term follow-up study (n=94).
- The evidence suggests that unlicensed melatonin products, taken for ten days to four weeks, may reduce sleep onset latency (the time taken for a child to go to sleep) in children with sleep onset insomnia and ADHD by approximately 20 minutes.
- In addition, melatonin may improve average sleep duration by 15 to 20 minutes. However, there are limitations to these small studies, and longer-term efficacy is unclear.
- These RCTs included stimulant and non-stimulant treated children aged six to 14 years with ADHD and suffering from sleep onset insomnia. The studies used daily doses of between 3 and 6mg of unlicensed melatonin described as 'fast-release' or 'short-acting', administered shortly before bedtime.
- Associated improvement in ADHD-related behaviour, cognition or quality of life was not robustly demonstrated.
- Unlicensed melatonin used in the RCTs appeared well tolerated in the short to medium term with only transient mild to moderate adverse effects reported.

NICE summarised that the evidence to support the use of melatonin in children and young people with ADHD is very limited.

## Shift work

The CKS on the management of shift work does not recommend the use of melatonin for this condition because:[19]

- Melatonin is not licensed for use in shift work disorders in the UK, and CKS considers that there is insufficient evidence to recommend its use.
- The American Academy of Sleep Medicine (AASM) reviewed the literature on shift work disorders and found two high quality randomised controlled trials (both simulation studies), and five field studies (one high, three moderate, one low quality). They concluded that melatonin improved sleep in some of the workers but did not increase night time alertness.[21]

## Safety concerns and treatment review

Evidence for the safety of melatonin is less well described than for other hypnotics.[5] Yet, usage has increased possibly due to concerns over the use of benzodiazepine and "Z drug" hypnotics. Prescribers are advised to only use hypnotics if insomnia is severe, using the lowest dose that controls symptoms for the shortest period of time. Review and, if appropriate, optimise prescribing of hypnotics to ensure that it is in line with national guidance.

The NICE Key Therapeutic Topic on Hypnotics[5] states that the risks associated with the long-term use of benzodiazepine and 'Z-drug hypnotics' have been well recognised for many years. Recent data also suggest a similar safety concern with melatonin. These risks include falls, accidents, cognitive impairment, dependence and withdrawal symptoms, and an increased risk of dementia.[5] An observational study found that in people aged 45 years and over, receiving three or more melatonin prescriptions were associated with an increased risk of fracture compared with no use of any hypnotic drugs.[5] For the 21% of participants who received three or more melatonin prescriptions, the average number of prescriptions was 11.9. The average age of participants in the study was 65 years and the average time of study follow-up was 2.6 years.[25] The NICE Medicines Evidence Commentary notes that "since its launch in 2008, prescribing of melatonin has increased in recent years; one possible reason for this could be due to safety concerns over benzodiazepine and 'Z drug' hypnotics. However, this study suggests that melatonin may also have similar risks when prescribed as a hypnotic in older people."[25] Circadin® 2mg P/R tablets should only be given for up to 13 weeks in total and so people receiving more than 13 weeks worth of prescriptions would be using melatonin outside of recommended treatment intervals. This emphasises the importance of stopping treatment within recommended treatment intervals for safety reasons.[6,15]

Little is known about the long-term effects (more than two years treatment) of melatonin in children. There is uncertainty on what effects exogenous melatonin has on other circadian rhythms including endocrine or reproductive hormone secretion.[10] There are some concerns that long-term use of melatonin might delay children's sexual maturation, possibly by disrupting the decline in nocturnal melatonin levels that occur at the onset of puberty. The European Public Assessment Report (EPAR) states that the long-term safety of up to two years of melatonin in children at doses of between 2mg and 10mg daily is in line with the known safety profile of Circadin® in adults and children (post-marketing experience). The EPAR states that there is a need for more long-term safety data on the safety of melatonin in general and more specifically related to pubertal development.[11] The SPC for Circadin® states that treatment may be continued for up to 13 weeks.[6] Any patients receiving Circadin® for more than 13 weeks should have their treatment reviewed.

In children, the need to continue melatonin therapy should be reviewed every six months.[10] Treatment with Slenyto® P/R tablets should be reviewed within the first three months of treatment. If no clinically relevant treatment effect is seen, consideration should be given to stopping treatment. If reduced outcomes are seen after a dose increase, reducing the dose again may be tried before completely stopping treatment. Treatment data is available for up to two year's treatment. Children on melatonin for over two years should have their treatment reviewed. Consider a dosage reduction or trial withdrawal of treatment.

Melatonin 1mg/ml oral solution (Colonis Pharma Ltd) should not be used in children and adolescents due to safety and efficacy concerns.[3] Melatonin 1mg/ml oral solution (Colonis Pharma Ltd) contains the following excipients which may be potentially problematic when used in children:[3,8]

- Propylene glycol 150.37 mg per 1ml dose
- Sorbitol 140 mg per 1ml dose

The total daily dose of excipients needs to be calculated and checked whether they are within the safety limits for the age and weight if melatonin 1mg/ml oral solution (Colonis Pharma Ltd) is being considered for use in a child.[8]

Table 2 lists excipients used in melatonin 1mg/ml oral solution (Colonis Pharma Ltd) with their safety limit (maximum daily dose) by child's age group. The total daily dose of excipient should be calculated and checked against these safety limits. Example calculations are included in table 2.

**Table 2. Melatonin 1mg/ml oral solution (Colonis Pharma Ltd) excipient quantities and safety limit (maximum daily dose) checks when used in children**[3,8,26,27]

| Excipient | Amount in melatonin 1mg/ml oral solution (Colonis Pharma Ltd) | Child's age group | Safety limit (maximum daily dose) | Example calculations and checks |
|---|---|---|---|---|
| Propylene glycol | 150.37mg per 1ml | Children aged 1 month - 4 years | 50mg/kg | The maximum daily dose of propylene glycol for a two year old weighing 16kg is 800mg. This is contained in 5.3ml of melatonin 1mg/ml oral solution (Colonis Pharma Ltd). The safety limit would be exceeded in doses of melatonin over 5.3mg.<br>The maximum daily dose of propylene glycol for a four year old weighing 23kg is 1150mg. This is contained in 7.65ml melatonin 1mg/ml oral solution (Colonis Pharma Ltd). The safety limit would be exceeded in doses of melatonin over 7.65mg. |
| | 150.37mg per 1ml | Children aged 5–17 years | 500mg/kg | The maximum daily dose of propylene glycol for a five year old weighing 27kg is 13.5g. This is contained in 89.8mls melatonin 1mg/ml oral solution (Colonis Pharma Ltd). The safety limit would not be reached at melatonin doses of 10mg and under. |

| Excipient | Amount in melatonin 1mg/ml oral solution (Colonis Pharma Ltd) | Child's age group | Safety limit (maximum daily dose) | Example calculations and checks |
|---|---|---|---|---|
| Sorbitol | 140 mg per 1ml | All ages of children | An oral dose of greater than 140mg/kg/day may result in gastrointestinal symptoms.<br>The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. | Melatonin 1mg/ml contains 140mg of sorbitol per ml. A 10kg child may have gastrointestinal symptoms with doses of sorbitol over 1400mg. 1400mg of sorbitol is contained in 10ml of melatonin 1mg/ml oral solution (Colonis Pharma Ltd).<br>It is important to consider the additive effects of sorbitol from other medicines or dietary sources. |

Patients on unlicensed melatonin need to be reviewed regularly for the continued need for treatment and monitoring of adverse effects. Although there is no guidance available for these products in terms of review intervals, a pragmatic approach is to follow recommendations made in the guidance for Circadin® for adults and Slenyto® for children. So, unlicensed melatonin preparations prescribed for adults would be reviewed after 13 weeks. Children prescribed an unlicensed melatonin preparation would be reviewed after the initial three months treatment, then six monthly for up to two years treatment duration.

During the treatment review, patients on unlicensed melatonin formulations should also be considered for a switch to an alternative formulation as outlined in table 3, on page 12, for quality, safety and cost-effectiveness reasons.

## Licensing considerations and product selection

Some patients have difficulty taking tablets or require doses not available in a licensed tablet form. They are prescribed an unlicensed melatonin preparation to meet their special clinical need. A total of 157,419 items of 42 different types of unlicensed melatonin preparations were prescribed across England and Wales from Jan-Dec 2018 (ePACT2). These included:

- Melatonin oral solution 2mg/5ml, 2.5mg/5ml, 3mg/5ml, 5mg/5ml
- Melatonin oral suspension 3mg/5ml, 5mg/5ml, 10mg/5ml
- Melatonin liquid special 1mg/5ml
- Melatonin capsules 500 micrograms, 1mg, 2mg, 2.5mg, 3mg, 4mg, 5mg, 6mg, 7mg, 8mg, 10mg, 20mg
- Melatonin tablets 500 micrograms, 1mg, 3mg, 5mg, 10mg
- Melatonin modified release tablets 3mg
- Melatonin modified release capsules 2mg

Unlicensed melatonin preparations are obtained from special manufacturers or are imported products. They are not required to undergo the same rigorous quality assurance processes as licensed preparations. Importers must ensure customers are aware of the origins of the products they are importing.[28] Some of these imported products are classified as supplements, not pharmaceuticals in their country of origin. Supplements do not need to meet the same rigorous quality assurance processes as pharmaceuticals because they do not have to be made under conditions of good pharmaceutical manufacturing practice. Melatonin oral preparations were the most frequently notified unlicensed imported medicine from 1 October 2018 to 31 December 2018 with 2,910 notifications. They accounted for 12.85% of all unlicensed imported medicines notified to the MHRA.[29]

It is preferable to use licensed preparations, which have quality, efficacy and safety data, rather than using unlicensed medicines or supplements. The BNF for Children (BNFC) states that there is variability in clinical effect of unlicensed formulations.[10] The MHRA advises that an unlicensed medicinal product should not be supplied where an equivalent licensed medicinal product can meet the special needs of the patient.[7]

Unlicensed melatonin preparations should therefore only be used as a last resort.

For patients with swallowing difficulties there are several preferred options which should be considered before using an unlicensed melatonin preparation. These include:

- For an immediate release dose: Halved, quartered or crushed Circadin® P/R 2mg tablets, Slenyto® P/R 1mg, or 5mg tablets, melatonin 3mg tablets or melatonin 1mg/ml oral solution (Colonis Pharma Ltd).
- For a prolonged-release melatonin dose: Mixing Slenyto® P/R 1mg or 5mg tablets with yoghurt, orange juice or ice-cream taken immediately to aid swallowing. Do not break, crush or chew them. If this is not suitable for the patient, then change to an immediate release preparation as above.

Where an immediate release form of melatonin is required, off-label use of halved, quartered or crushed Circadin® P/R tablets or Slenyto® P/R tablets; melatonin 3mg tablets or melatonin 1mg/ml oral solution (Colonis Pharma Ltd) should be tried before, and is preferable to, using an unlicensed liquid melatonin formulation.[7]

When a prolonged-release tablet is crushed, the manufacturers have advised that the in-vitro release from a crushed or powdered prolonged-release tablet is expected to provide an immediate release profile like that from an unlicensed immediate release tablet or oral liquid formulation. This makes halving, quartering or crushing a P/R tablet a viable alternative to immediate release tablets or liquid formulations. Unlicensed melatonin liquid formulations, tablets and capsules are examples of immediate release formulations.

Melatonin has a naturally short half-life which is why a prolonged-release formulation was developed to achieved sustained melatonin levels during sleep. Prolonged release tablets have a slower rate of absorption and a lower peak plasma concentration, but a greater overall extent of absorption than melatonin solution.[11] Wherever possible, the patient should be encouraged to swallow the P/R tablets whole to benefit from the prolonged-release of melatonin. For patients with swallowing difficulties, Slenyto® P/R tablets are small with a diameter of 3mm and can be mixed into food such as yoghurt, orange juice or ice-cream to aid swallowing.

Melatonin 3mg tablets and melatonin 1mg/ml oral solution (Colonis Pharma Ltd) are licensed for use in adults, (aged 18 years and over).[2,3] Circadin® is licensed for use in those aged 55 years and over.[6] Slenyto® is licensed for use in children aged 2–18 years.[1] Use outside of these age restrictions for each of these preparations would be off-label uses.

Table 3 shows examples of melatonin presentations and uses and their licence status. Suggested actions are listed in line with MHRA advice on the supply of unlicensed medicinal products (specials) and treatment review recommendations. Patients prescribed unlicensed melatonin preparations should firstly be reviewed for the continued need for melatonin and then for suitability for a switch to a suggested action as outlined in table 3.

**Table 3. Licensing status of melatonin and suggested actions**[1-4,6,7]

| Melatonin presentation and use | License status | Suggested action |
|---|---|---|
| Circadin® monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over. | Licensed use of Circadin®[6] | Consider stopping treatment at 13 weeks. |
| Slenyto® for the treatment of insomnia in children and adolescents aged two to 18 years with Autism Spectrum Disorder (ASD) and/or Smith-Magenis syndrome where sleep hygiene measures have been insufficient. | Licensed use of Slenyto®[1] | Treatment review at three months, then six monthly for up to two years. Consider stopping treatment after two years. |
| Melatonin 3mg tablets or melatonin 1mg/ml oral solution (Colonis Pharma Ltd) for the short-term treatment of jet lag in adults - 3mg to 6mg daily for five days. | Licensed use of melatonin 3mg tablets/1mg/ml oral solution (Colonis Pharma Ltd)[2,3] | **No NHS prescriptions to be issued for use in jet lag in line with GMS Regulations.**[4]<br>GPs to issue private prescriptions if prescribing for this indication. |
| Melatonin 1mg/ml oral solution (Colonis Pharma Ltd) used in children. | Unlicensed use of melatonin 1mg/ml oral solution (Colonis Pharma Ltd) | Check that excipient safety limits have not been exceeded especially for children under 4 years old, e.g. melatonin doses greater than 5.3mg in a 2 year old or 7.65mg in a 4 year old.<br>Dose optimise and use:<br>Cut in half, quartered or crushed Circadin® P/R tablets, Slenyto® P/R tablets or melatonin 3mg tablets (Colonis Pharma Ltd) |
| Circadin® or Slenyto® use for a diagnosis outside their licensed indications, e.g. sleep disorders in ADHD without a concomitant disorder of ASD, shift work. | Off-label use of Circadin® or Slenyto® | Review effectiveness, adverse effects, consider licensed alternatives or stopping clinically inappropriate treatment. |
| Circadin® used in patients aged under 55 years or Slenyto® used in children under two or in those over 18 years and within their licensed indications. | Off-label use of Circadin® or Slenyto® | Review effectiveness, adverse effects, consider licensed alternatives or stopping clinically inappropriate treatment. |

| Melatonin presentation and use | License status | Suggested action |
|---|---|---|
| Circadin® or Slenyto® tablets crushed and used for licensed indication. | Off-label use of Circadin® or Slenyto® | Treatment reviews at recommended intervals for each product. |
| Circadin® given at dose greater than 2mg, Slenyto® given at dose greater than 10mg, melatonin 3mg tablets or melatonin 1mg/ml oral solution (Colonis Pharma Ltd) at a dose greater than 6mg and for more than five days treatment and/or 16 treatment courses per year. | Off-label use of Circadin® or Slenyto® or melatonin 3mg tablets or melatonin 1mg/ml oral solution (Colonis Pharma Ltd) | Review effectiveness, reduce melatonin dose, consider stopping if ineffective. |
| Melatonin standard release tablets/capsules (unlicensed). | Unlicensed medicine[7] | Dose optimise and use:<br>• Melatonin 3mg tablets (Colonis Pharma Ltd)<br>• Cut in half, quartered or crushed Circadin® P/R tablets or Slenyto® P/R tablets<br>• Melatonin 1mg/ml oral solution (Colonis Pharma Ltd) |
| Melatonin PR/modified release tablets/capsules with exception of Circadin® or Slenyto®. | Unlicensed medicine[7] | Dose optimise and use Circadin® or Slenyto® tablets. |
| Melatonin oral solution/liquid (unlicensed). | Unlicensed medicine[7] | Dose optimise and use:<br>• Cut in half, quartered or crushed Circadin® P/R tablets, Slenyto® P/R tablets or melatonin 3mg tablets (Colonis Pharma Ltd)<br>• Melatonin 1mg/ml oral solution (Colonis Pharma Ltd) |

## Costs and savings

The annual spend on melatonin across England and Wales is **£30 million for 972,708 items prescribed. £7.8 million of this is for unlicensed melatonin preparations** (ePACT2 Feb 2019-Apr 2019).

The introduction of licensed versions of melatonin in children (Slenyto®), licensed melatonin tablets and oral solution could result in further prescribing items and cost increases.

## Review treatment with melatonin

Adults and children prescribed melatonin, both licensed and unlicensed uses, need to be reviewed regularly for the continued need for treatment and monitoring of adverse effects. A 40% reduction in all melatonin prescribing (reviewing treatment and discontinuing therapy that is no longer appropriate/ using non drug measures first line) **could release savings of £12 million per year in England and Wales. This equates to £19,066 per 100,000 population in England and Wales.**

## Review melatonin preparations prescribed for children

Approximately 60% of melatonin items were prescribed for use in children and accounted for 74% of total melatonin spend. The melatonin average cost per item for adults over 20 years old is £19.44. The melatonin average cost per item for ages 0-19 years old is £37.61 which is £18.17 (48%) more than prescriptions for adults over 20 years old. Most melatonin prescriptions (85%) are for the licensed Circadin® brand or written by the generic name melatonin 2mg M/R tablets (ePACT2 Sept 17-Aug 18).

It is unknown how much of the current paediatric use is for children with ASD or SMS. Any use of Slenyto® outside of the licensed use would be off-label, just as the use of Circadin®, melatonin 3mg tablets, melatonin 1mg/ml oral solution (Colonis Pharma Ltd) in children would be off-label.

Slenyto® prolonged-release tablets are available in two strengths, 1mg and 5mg. To achieve a 2mg dose, two 1mg Slenyto® tablets will need to be prescribed. This increases costs compared to Circadin® 2mg P/R tablets and some unlicensed immediate release capsules or tablets. If children are switched from Circadin®/melatonin 2mg P/R tablets to two Slenyto® 1mg tablets this would **increase costs by £17.5 million per year across England and Wales or £27,979 per 100,000.**

It is recommended that children stabilised on Circadin® P/R tablets who do not fulfil the licensing criteria for Slenyto® should remain on Circadin® tablet for consistency and continuity reasons.

Patients meeting the Slenyto® licensed indications should have their treatment reviewed and switched to Slenyto® if appropriate for the individual patient. The melatonin preparation and dose used will need to be optimised in line with licensed doses and to manage the cost pressures arising from the introduction of Slenyto®. The recommended starting dose for Slenyto® is 2mg. If needed, the dose is increased to 5mg, then to a maximum dose of 10mg. If a lower treatment effect is seen after titration to a higher dose of melatonin, first consider a down-titration to a lower dose before deciding on a complete discontinuation of treatment. For example, patients recently increased to 5mg should be lowered back to 2mg and patients recently increased to 10mg should be lowered back to 5mg.

The costs of different doses of Circadin® P/R tablets, Slenyto® tablets, melatonin 3mg tablets and melatonin 1mg/ml oral solution (Colonis Pharma Ltd) are shown in table 4, on page 15.

Table 4 can be used to highlight cost-effective preparations for an individual patient and to help with dose optimisation decisions. Table 4 provides colour coding for easy detection of licensed and unlicensed doses of melatonin.

**Table 4. Cost comparison for different doses of Circadin®, Slenyto®, Melatonin 3mg tablets (Colonis Pharma Ltd) and melatonin 1mg/ml oral solution (Colonis Pharma Ltd) preparations[30,31]**

| Melatonin daily dose | Strength and number of doses per day | Cost per 28 days[30,31] |
|---|---|---|
| 1mg | Slenyto® 1mg P/R tablets x 1 | £19.23 |
| 1mg | Melatonin 1mg/ml oral solution 1ml | £24.27* |
| 2mg | Circadin® 2mg P/R tablets x 1 | £14.28 |
| 2mg | Slenyto® 1mg P/R tablets x 2 | £38.46 |
| 2mg | Melatonin 1mg/ml oral solution 2ml | £48.54* |

| Melatonin daily dose | Strength and number of doses per day | Cost per 28 days[30,31] |
|---|---|---|
| 3mg | Melatonin 3mg tablets x 1 | £60.67* |
| 3mg | Melatonin 1mg/ml oral solution 3ml | £72.81* |
| 3mg | Slenyto® 1mg P/R tablets x 3 | £57.69 |
| 4mg | Circadin® 2mg P/R tablets x 2 | £28.56 |
| 4mg | Slenyto® 1mg P/R tablets x 4 | £76.92 |
| 4mg | Melatonin 1mg/ml oral solution 4ml | £97.08* |
| 5mg | Slenyto® 5mg P/R tablets x 1 | £96.13 |
| 5mg | Melatonin 1mg/ml oral solution 5ml | £121.35* |
| 6mg | Melatonin 3mg tablets x 2 | £121.34* |
| 6mg | Melatonin 1mg/ml oral solution 6ml | £145.62* |
| 6mg | Circadin® 2mg P/R tablets x 3 | £42.84 |
| 6mg | Slenyto®1mg P/R tablets x 1 & Slenyto® 5mg P/R tablets x 1 | £115.36 |
| 7mg | Slenyto®1mg P/R tablets x 2 & Slenyto® 5mg P/R tablets x 1 | £134.59 |
| 7mg | Melatonin 1mg/ml oral solution 7ml | £169.89 |
| 8mg | Circadin® 2mg P/R tablets x4 | £57.12 |
| 8mg | Slenyto®1mg P/R tablets x 3 & Slenyto® 5mg P/R tablets x 1 | £153.82 |
| 8mg | Melatonin 1mg/ml oral solution 8ml | £194.16 |
| 9mg | Melatonin 3mg tablets x 3 | £182.01 |
| 9mg | Melatonin 1mg/ml oral solution 9ml | £218.43 |
| 10mg | Circadin® 2mg P/R tablets x 5 | £71.40 |
| 10mg | Slenyto® 5mg P/R tablets x 2 | £192.26 |
| 10mg | Melatonin 1mg/ml oral solution 10ml | £242.70 |

| Colour code | Licensed doses | |
|---|---|---|
| | Unlicensed doses | |

*Only licensed for a maximum of five days treatment and 16 treatments per year.[2,3]

## Review unlicensed melatonin preparations

Switching from an unlicensed to a licensed preparation is preferred from a quality and safety perspective. In some circumstances it is also a cost saving switch. Patients should be switched to the licensed preparation where suitable for the individual.

Table 5 looks at the impact of switching the most frequently used unlicensed melatonin preparations to either Circadin® P/R tablets, licensed melatonin 3mg tablets (Colonis Pharma Ltd), licensed melatonin 1mg/ml oral solution (Colonis Pharma Ltd) or Slenyto® P/R tablets and are expressed as cost avoidance or cost pressure percentages. Cost pressures are negative percentages. Using Circadin®, licensed melatonin 3mg tablets / 1mg/ml oral solution (Colonis Pharma Ltd) or Slenyto® in preference to unlicensed medicines would be in line with MHRA recommendations on using licensed preparations and provide reassurance around the quality of the product. In some cases, a switch away from the unlicensed medicine would be a cost pressure and use may be off-label. The impact of this potential cost pressure can be reduced by choosing the most cost-effective option suitable for the individual patient.

**Table 5. Unlicensed melatonin switch to licensed melatonin preparations cost avoidance/cost pressure without dose optimisation[30,31]**

| Unlicensed melatonin preparation | % cost avoidance/ (cost pressure) if switched to licensed melatonin 3mg tablets (Colonis Pharma Ltd) | % cost avoidance/ (cost pressure) if switched to licensed melatonin 1mg/ml oral solution (Colonis Pharma Ltd) | % cost avoidance/ (cost pressure) if switch to Circadin® 2mg tablets | % cost avoidance/ (cost pressure) if switch to Slenyto® 1mg or 5mg tablets |
|---|---|---|---|---|
| Melatonin 2mg capsule | 43% | 54% | 86% | 64% |
| Melatonin 3mg capsule | 45% | 35% | 81% | 48% |
| Melatonin 3mg tablets | 43% | 32% | 80% | 46% |
| Melatonin 3mg M/R capsule | 49% | 38% | 82% | 51% |
| Melatonin 1mg capsule | 33% | 73% | 92% | 79% |
| Melatonin tablet 1mg | 29% | 71% | 92% | 77% |
| Melatonin capsule 2.5mg | 50% | 50% | 82% | 53% |
| Melatonin tablet 5mg | 4% | 4% | 72% | 24% |
| Melatonin oral suspension 2.5mg/5ml | 14% | 14% | 70% | 19% |
| Melatonin liquid special 1mg/5ml | 77% | 91% | 97% | 93% |
| Melatonin capsule 2mg M/R | 31% | 45% | 84% | 56% |
| Bio-Melatonin 3mg tablets | 15% | -2% | 70% | 20% |
| Melatonin oral suspension 2mg/5ml | -8% | 14% | 75% | 32% |
| Melatonin oral suspension 3mg/5ml | 13% | -4% | 69% | 18% |
| Melatonin oral solution 2.5mg/5ml | -9% | -9% | 62% | -4% |
| Melatonin 5mg capsule | -37% | -37% | 60% | -8% |
| Melatonin oral solution 2mg/5ml | -75% | -40% | 59% | -11% |
| Melatonin oral suspension 10mg/5ml | -86% | -272% | -9% | -195% |
| Melatonin oral solution 10mg/5ml | -90% | -279% | -11% | -200% |

| Unlicensed melatonin preparation | % cost avoidance/ (cost pressure) if switched to licensed melatonin 3mg tablets (Colonis Pharma Ltd) | % cost avoidance/ (cost pressure) if switched to licensed melatonin 1mg/ml oral solution (Colonis Pharma Ltd) | % cost avoidance/ (cost pressure) if switch to Circadin® 2mg tablets | % cost avoidance/ (cost pressure) if switch to Slenyto® 1mg or 5mg tablets |
|---|---|---|---|---|
| Melatonin 10mg capsule | -22% | -144% | 28% | -93% |
| Melatonin oral suspension 5mg/5ml | -250% | -250% | -3% | -177% |
| Melatonin oral solution 5mg/5ml | -216% | -215% | 7% | -150% |

**Cost pressures are highlighted in red.**

Switching from unlicensed melatonin preparations to Circadin® **could save £6 million per year in England and Wales or £9,594 per 100,000 population.**

Switching from unlicensed melatonin preparations to Slenyto® **could save £3.1 million per year in England and Wales or £5,009 per 100,000 population.**

## Summary

- Melatonin is widely used and yet it has narrow licensed uses.
- Melatonin has been included in warnings on adverse effects with other hypnotics.
- Treatment duration is intended to be short and so it is important that patients continued need for treatment is reviewed at appropriate intervals.
- Treatment should be stopped in discussion with the individual if it is ineffective, producing adverse effects or no longer required.
- Slenyto® was recently licensed for use in children.
- Melatonin 3mg tablets and 1mg/ml oral solution (Colonis Pharma Ltd) were recently licensed for the short-term treatment of jet lag in adults.
- NHS prescriptions for melatonin should not be issued for anticipatory use for jet lag.
- Melatonin 1mg/ml oral solution (Colonis Pharma Ltd) should not be used in children and adolescents due to safety and efficacy concerns.[3]
- Prescribers should review the use of unlicensed melatonin preparations with a view to switching patients to a cost-effective licensed alternative suitable for the individual patient.
- Melatonin doses need to be optimised to manage any potential cost increases when switching melatonin preparations.

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## Additional PrescQIPP resources

| | |
|---|---|
| Bulletin | https://www.prescqipp.info/our-resources/bulletins/bulletin-245-melatonin/ |
| Implementation tools | |
| Data pack | https://pdata.uk/#/views/B245_Melatonin/FrontPage?:iid=1 |

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