The East of England
Priorities Advisory Committee
Hosted by PrescQIPP

GUIDANCE STATEMENT

Melatonin (Slenyto®) 1mg and 5mg prolonged-release tablets

PAC recommendations

- **Commissioning of melatonin (Slenyto®) for the treatment of insomnia in children and adolescents aged two to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient, is not recommended as the case for cost effectiveness has not been proven.**
- **Off label use for any other indication is not recommended.**
- **These recommendations with be reviewed in the light of new evidence on cost effectiveness.**

Key points

- Melatonin (Slenyto®) is licensed for the treatment of insomnia in children and adolescents aged two to 18 years with Autism Spectrum Disorder (ASD) and/or Smith-Magenis Syndrome (SMS), where sleep hygiene measures have been insufficient.[1,2]
- There are currently no other licensed pharmacological treatments for the above indications in the UK. The main treatments available are non-drug treatments, including good sleep hygiene measures. If sleep problems continue despite appropriate behavioural sleep interventions, adjunctive pharmacotherapy is often prescribed. The off-label use of prolonged-release (PR) melatonin (Circadin®) and unlicensed immediate-release (IR) melatonin preparations is established practice nationally.
- The Scottish Medicines Consortium (SMC) do not recommend melatonin (Slenyto®) for use within Scotland. The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient, and in addition the company did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC.[3]
- The All Wales Medicine Strategy Group (AWMSG) do not recommend melatonin (Slenyto®) for use within NHS Wales as the case for cost-effectiveness has not been proven.[4]
- In line with the SMC and AWMSG, PAC do not recommend the use of melatonin (Slenyto®) for the treatment of insomnia in children and adolescents aged two to 18 years with ASD and/or SMS, where sleep hygiene measures have been insufficient as the case for cost effectiveness has not been proven.

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. Slenyto® is the first EU-licensed paediatric specific preparation of PR melatonin for the treatment of insomnia in children and adolescents aged two to 18 years with ASD and/or SMS, where sleep hygiene measures have been insufficient.[5]

- Slenyto® was granted marketing authorisation by the European Medicines Agency (EMA) in September 2018, and is formulated as a 1mg or 5mg, film-coated mini tablet for once-daily administration, which can be put into food such as yoghurt, orange juice or ice-cream to help with swallowing. The tablets should be swallowed whole and not broken, crushed or chewed. Melatonin (Slenyto®) is licensed for the treatment of insomnia in children and adolescents aged two to 18 years with ASD and/or SMS, where sleep hygiene measures have been insufficient. The recommended starting dose of Slenyto® is 2mg once daily, with a maximum dose of 10mg.[1,2]
- There are currently no other licensed pharmacological treatments for the treatment of insomnia in children and adolescents aged two to 18 years with ASD and/or SMS. The off-label use of PR melatonin (Circadin®) and unlicensed IR melatonin preparations is established practice nationally.

Clinical effectiveness

- Efficacy and safety of Slenyto® have been demonstrated in a randomised, placebo-controlled study in children diagnosed with ASDs and neurodevelopmental disabilities caused by SMS who had not shown improvement after standard sleep behavioural intervention.[1,2]
- The SMC summarised the evidence for clinical efficacy in their review in August 2019.[3] In the main study melatonin PR (Slenyto®), compared with placebo, increased total sleep time by about 30 minutes on average and reduced sleep onset latency by about 25 minutes, which were considered clinically relevant by the EMA. However, it did not significantly improve the number of awakenings or duration of wake time (in contrast to expectations associated with a PR preparation). The effects on total sleep time and sleep onset latency were maintained in assessments up to 52 weeks.[3]
- The study did not generate objective measurements of sleep (as secondary outcomes) as many of the children refused to wear actigraph watches.[3,6] There was no other objective evidence, for example from polysomnography, in the submission. However, EMA guidance on the investigation of medicinal products for the treatment of insomnia notes that there can be poor correlation between these objective outcomes and patients' subjective assessments and recommends that phase III studies be conducted in natural settings. This guideline also recommends that benefits should be demonstrated in daytime functioning. In the melatonin prolonged-release (Slenyto®) study, changes in social functioning and behaviour at home and school, measured using the Children's Global Assessment Scale (CGAS) and Strengths and Difficulties Questionnaire (SDQ) (total score), were small and similar to those in the placebo group. Only the SDQ sub-domain of 'externalising behaviours' was significantly positively affected in the study. The EMA noted that the improved well-being of the parents supported a beneficial effect of melatonin prolonged release (Slenyto®).[3,6]
- The main study included only four patients (3.2%) with neurogenetic disorders (all four patients had SMS) and provides limited data in children with these conditions. However, the EMA review noted evidence from studies of other melatonin preparations in neurogenetic disorders.[3,6] The majority of patients in the study had sleep onset problems (96%), with many of these also having sleep maintenance problems (56%). The study does not provide evidence of efficacy in patients who only experienced sleep maintenance problems, as these patients comprised less than 4% of the study population.[3]
- The All Wales Therapeutic and Toxicology Centre Secretariat Assessment Report and the SMC did not identify any efficacy or safety studies comparing Slenyto® with off-label or unlicensed melatonin products.[3,5]

Cost effectiveness

- A literature review conducted by All Wales Therapeutic and Toxicology Centre (AWTTC) did not identify any studies relevant to the cost-effectiveness of Slenyto® versus IR melatonin in the treatment of patients with insomnia in the specified patient population.[5]
- The AWTTC appraised a submission from Flynn Pharma Ltd. The company submission included a cost-utility analysis comparing oral administration of Slenyto® 1mg and 5mg PR melatonin with a comparator bundle of IR melatonin (unlicensed capsules, tablets and oral solution), for the treatment of insomnia in children and adolescents aged two to 18 years with ASD and/or SMS, where sleep hygiene measures have been insufficient (i.e. the full licensed indication).[5]
- The AWTTC appraisal was used as the basis for the AWMSG commissioning decision. In reaching their commissioning decision, the AWMSG considered the use of a cost-utility analysis was appropriate however noted several limitations and uncertainties, including the absence of the main comparator (off-label Circadin®), The AWMSG questioned the utility assumptions and noted structural and parameter uncertainty in the model. They concluded that the case for cost-effectiveness has not been proven and do not recommend for use in Wales.[4,5]
- The SMC considered a cost-utility analysis submitted by the manufacturers which compared melatonin prolonged-release (Slenyto®) tablets with melatonin IR (Bio-melatonin®) tablets. The committee concluded that the analysis was associated with a number of important weaknesses including that key comparators within Scotland (Circadin® and generic IR melatonin) were not included in the company's submission. After considering all the available evidence, the Committee was unable to accept melatonin prolonged-release (Slenyto®) for use in NHS Scotland.[3]
- The National Institute for Health and Care Excellence (NICE) do not make any specific recommendations on the use of melatonin (Slenyto®).[7]
- In line with the SMC and AWMSG recommendations, PAC do not recommend the use of melatonin (Slenyto®) for the treatment of insomnia in children and adolescents aged two to 18 years with ASD and/or SMS, where sleep hygiene measures have been insufficient as the case for cost effectiveness has not been proven.

Cost impact

- 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 all 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**.[8]

Document history

PAC approval date	6th July 2020
Version	1
Consultation process	PAC members East of England clinicians
QA process	Katie Smith, Director of Clinical Quality, PrescQIPP 4th August 2020

References

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2. SPC Slenyto 5mg. Flynn Pharma Ltd. Last updated 8th June 2020. Accessed 12th February 2020. https://www.medicines.org.uk/emc/product/10024/smpc
3. Scottish Medicines Consortium. Advice on the use of melatonin 1mg and 5mg prolonged-release tablets (Slenyto®). Published 9th August 2019. https://www.scottishmedicines.org.uk/medicines-advice/melatonin-slenyto-full-smc2168/
4. All Wales Medicines Strategy Group. Final Appraisal Recommendation. Melatonin (Slenyto®) 1mg and 5mg prolonged-release tablets. Advice No: 1519 – Published November 2019. https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/melatonin-slenyto/
5. All Wales Therapeutic and Toxicology Centre Secretariat Assessment Report. Melatonin (Slenyto®) 1mg and 5mg prolonged-release tablets. Reference number: 3947. Published November 2019. https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/melatonin-slenyto/
6. European Medicines Agency (EMA). European public assessment report, Committee for Medicinal Products for Human Use (CHMP) assessment report for Slenyto, EMA/556280/2018. Published 26 July 2018. https://www.ema.europa.eu/en/medicines/human/EPAR/slenyto
7. National Institute for Health and Care Excellence https://www.nice.org.uk Accessed 2nd March 2020
8. PrescQIPP Bulletin 245: Melatonin. Published February 2020. https://www.prescqipp.info/our-resources/bulletins/bulletin-245-melatonin/

Appendix 1: Assessment against ethical and commissioning principles

Treatment assessed

Melatonin (Slenyto®) for the treatment of insomnia in children and adolescents aged two to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient, is not recommended as the case for cost effectiveness has not been proven.

East of England Priorities Advisory Committee Recommendation TBC:

Commissioning of melatonin (Slenyto®) for the treatment of insomnia in children and adolescents aged two to 18 years with ASD and/or SMS, where sleep hygiene measures have been insufficient, is not recommended as the case for cost effectiveness has not been proven.

Clinical effectiveness

Efficacy and safety have been demonstrated in a randomised, placebo-controlled study in children diagnosed with ASDs and neurodevelopmental disabilities caused by SMS who had not shown improvement after standard sleep behavioural intervention. No studies comparing the efficacy or safety of Slenyto® with off-label or unlicensed melatonin products have been identified.

Cost effectiveness

Cost effectiveness of melatonin (Slenyto®) has not been proven.

Equity

None identified.

Needs of the community

The needs of the community are considered to be low as established alternative treatments exist.

Need for healthcare (incorporates patient choice and exceptional need)

Well established alternative treatments exist.

Policy drivers

All Wales Medicines Strategy Group. Final Appraisal Recommendation. Melatonin (Slenyto®) 1mg and 5mg prolonged-release tablets. Advice No: 1519 – November 2019. https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/melatonin-slenyto/

Scottish Medicines Consortium. Advice on the use of melatonin 1mg and 5mg prolonged-release tablets (Slenyto®). 9th August 2019. https://www.scottishmedicines.org.uk/medicines-advice/melatonin-slenyto-full-smc2168/

Disinvestment

Increased costs of using melatonin (Slenyto®) in place of established treatments are significant. Use may result in funding being diverted from other healthcare priorities.