

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

Flynn Pharma Ltd

4 December 2020

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a resubmission

**melatonin prolonged-release (Slenyto®)** is not recommended for use within NHSScotland.

**Indication under review:** Treatment of insomnia in children and adolescents aged 2 to 18 years with autism spectrum disorder and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.

Melatonin prolonged-release (Slenyto®), compared with placebo, increased total sleep time and sleep onset latency in children aged 2 to 17.5 years with sleep problems and autism spectrum disorder and / or Smith-Magenis syndrome who had an insufficient response to sleep hygiene measures.

The company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

**Chairman**  
**Scottish Medicines Consortium**

## Indication

Treatment of insomnia in children and adolescents aged 2 to 18 years with autism spectrum disorder and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.<sup>1</sup>

## Dosing Information

Initially melatonin 2mg orally once daily, 0.5 to 1 hour before bedtime. The tablet should be swallowed whole with or after food. It should not be broken, crushed or chewed because it will lose the prolonged release properties. If there is an inadequate response, the dose can be increased to 5mg, with a maximum of 10mg.

Data are available for up to 2 years' treatment.

The patient should be monitored at regular intervals (at least every 6 months) to check that melatonin is still the most appropriate treatment. After at least 3 months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. If a lower treatment effect is seen after titration to a higher dose, the prescriber should first consider a down-titration to a lower dose before deciding on a complete discontinuation of treatment.<sup>1</sup>

## Product availability date

April 2019

## Summary of evidence on comparative efficacy

The activity of melatonin at the melatonin receptors (MT1, MT2 and MT3) is believed to contribute to its sleep-promoting properties, as these receptors (mainly MT1 and MT2) are involved in the regulation of circadian rhythms and sleep regulation.<sup>1</sup>

A double-blind phase III study recruited children and young people aged 2 to 17.5 years with an autism spectrum disorder diagnosed by the International Classification of Diseases 10<sup>th</sup> revision (ICD-10), Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) or DSM-4 criteria and at least 3 months of sleep problems, defined as 6 or fewer hours of continuous sleep and/or at least 30 minutes of sleep latency from lights-off on 3 out of 5 nights based on parent reports and past medical history. Patients without a documented history of sleep behavioural intervention underwent a 4-week parent-led sleep behavioural intervention. During this period there was wash-out of any other hypnotic medicines. Patients who still had sleep problems following a 2-week single-blind placebo run-in were then randomised equally to 13 weeks double-blind treatment with melatonin prolonged-release once daily (n=60) or placebo (n=65). The starting dose of melatonin was 2mg and this could be increased to 5mg after three weeks if the patient did not have an improvement of at least 1 hour measured by shortening of sleep latency and/or increase in total sleep time. The primary outcome was change from baseline (2-week placebo run-

in) in mean total sleep time from parent completed Sleep and Nap Diaries over the 14 days prior to study visit at week 13. This was assessed in the full analysis set, which comprised all randomised patients who received at least one dose of study drug, satisfied all major entry criteria and had assessments of mean total sleep time at baseline and at least one during double-blind treatment.<sup>2,3</sup>

Baseline total sleep time was just over 7.5 hours in both groups (457 minutes in the treatment group and 460 minutes in the control group). Melatonin prolonged-release (Slenyto<sup>®</sup>), compared with placebo, significantly improved change from baseline to week 13 in total sleep time (p=0.034). It also appeared to improve the secondary outcome of sleep onset latency, but had no effect on number of awakenings and duration of wake time as detailed in table 1.<sup>2,3</sup>

**Table 1: Primary and secondary outcomes at week 13.**

	Adjusted mean change from baseline		
	Melatonin	Placebo	Difference (95% CI)
Total sleep time (minutes)	51.16	18.73	32.43 (2.48, 62.38)
Sleep onset latency (minutes)	-37.88	-12.58	-25.3 (-44.7, -5.9)
Number of awakenings	-0.3	-0.2	-0.09 (-0.35, 0.16)
Duration of wake time (minutes)	-10.38	-10.30	-0.08 (-7.02, 6.86)
Longest sleep episode (minutes)	72.18	30.02	42.16 (-0.42, 84.73)

CI = confidence interval

Children’s Global Assessment Scale (CGAS) and Strength and Difficulties Questionnaire (SDQ) were used to assess social functioning and behaviour at home and school. Melatonin prolonged-release (Slenyto<sup>®</sup>) improved externalising behaviours (hyperactivity/ inattention and conduct scores), demonstrated by a treatment difference of -0.83 (95% confidence interval: -1.54 to -0.13), compared with placebo, in the SDQ at week 13. Changes from baseline in the total SDQ score and in the CGAS were small and were not significantly different between treatments.<sup>1,2</sup>

The treatment effects on sleep variables were associated with improved parents’ well-being, demonstrated by a treatment difference of 2.17 points (95% confidence interval: 0.53 to 3.82), compared with placebo, in the caregivers’ well-being 5-item World Health Organisation Well-Being Index (WHO-5) at week 13 (exploratory outcome).<sup>1,2</sup>

After 13 weeks of double-blind treatment patients could continue to receive treatment for a further 91 weeks in an open-label safety phase. Patients who had received melatonin 2mg and 5mg during double-blind treatment remained on these doses and patients who had received placebo 2mg and 5mg transferred to melatonin 2mg and 5mg, respectively, at the start of the open-label treatment phase. Dose escalation from 2mg to 5mg and 5mg to 10mg was permitted as required. There were 51 and 44 patients from the melatonin and placebo groups, respectively, who entered the open-label phase. After 13, 26 and 39 weeks’ of open-label treatment mean changes from baseline were significant for total sleep time, sleep onset latency, number of awakenings, longest sleep duration, quality of sleep and Composite Sleep Disturbance Index (CSDI) as detailed in table 2.<sup>2,4</sup>

**Table 2: Change from baseline after 13, 26 and 39 weeks in open-label phase.<sup>2,4</sup>**

	Estimated change from baseline		
	13 weeks N=91	26 weeks N=79	39 weeks N=72
Total sleep time (minutes)	37.01	40.75	44.35
Sleep onset latency (minutes)	-28.39	-41.9	-41.36
Number of awakenings	-0.35	-0.38	-0.39
Longest sleep duration (minutes)	64.21	76.0	78.63
Quality of sleep	0.53	0.67	0.72
Composite sleep disturbance index	-2.46	-3.12	-3.27

A Bucher indirect comparison of melatonin prolonged-release (Slenyto<sup>®</sup>) versus melatonin immediate-release was presented in the submission using data from the study described above and the MENDS study, which was a phase III randomised, double-blind comparison of melatonin immediate-release capsules and placebo.<sup>2,3,5</sup> The results suggest that melatonin prolonged-release (Slenyto<sup>®</sup>) is associated with an increased period of total sleep time relative to melatonin immediate-release.

### Summary of evidence on comparative safety

The most common adverse events associated with melatonin in children are fatigue and somnolence. There is a lack of long-term safety data, particularly relating to potential adverse effects in puberty.<sup>2</sup>

During the double-blind phase of the main study within the melatonin and placebo groups 85% (51/60) and 77% (50/65) of patients reported an adverse event, which was treatment-related in 20% and 17%, and serious adverse events were reported by 22% and 20%, respectively. The most common adverse events were somnolence (28% and 12%) and fatigue (25% and 18%) and these occurred at a higher rate in the melatonin group, as did agitation (18% and 11%) and headache (13% and 6.2%). Rates of upper respiratory tract infection (15% and 11%), cough (12% and 7.7%) and dyspnoea (10% and 6.2%) were a little higher in the melatonin group. Rates of other common adverse events were similar across the melatonin and placebo groups: mood swings (17% and 17%), vomiting (13% and 15%) and rash (5.0% and 4.6%).<sup>2,3</sup>

### Summary of clinical effectiveness issues

Sleep disorders are common in children with pervasive developmental disorders. These are often chronic and characterised by difficulties initiating or staying asleep and are usually more difficult to treat than in other children. Sleep disorders in children commonly impact on parents/ caregivers, affecting their day-time functioning and well-being.<sup>2</sup> Some children with neurodevelopmental disorders can have low endogenous levels of melatonin and abnormal

circadian rhythm. Children with the genetic disorder Smith-Magenis syndrome can have a severe phase shift in their circadian melatonin rhythm. Melatonin has a modulatory effect on sleep initiation and maintenance.<sup>2</sup> Melatonin prolonged-release (Slenyto<sup>®</sup>) is the first medicine to be licensed in the UK for the treatment of insomnia in children.<sup>1</sup>

Other melatonin prolonged release and immediate release preparations are available in the UK, licensed for the treatment of adults. Clinical experts consulted by SMC have advised that there is 'off-label' use of these medicines to treat insomnia in children. The Scottish Intercollegiate Guidelines Network (SIGN) suggest a trial of melatonin to improve sleep should be considered in children with autism spectrum disorders who have sleep difficulties which have not resolved following behavioural interventions.<sup>6</sup> Tablet formulations often have to be crushed for children with swallowing difficulties. Melatonin prolonged-release (Slenyto<sup>®</sup>) is available as 1mg and 5mg tablets offering increased flexibility of dosing in a small (3mm diameter) modified-release formulation.

In the main study melatonin prolonged-release (Slenyto<sup>®</sup>), 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 European Medicines Agency (EMA). An exploratory endpoint suggested melatonin treatment was associated with improvements in well-being of parents. However, it did not significantly improve the number of awakenings or duration of wake time (in contrast to expectations associated with a prolonged-release preparation).<sup>2,3</sup> The effects on total sleep time and sleep onset latency were maintained in assessments up to 52 weeks.<sup>2,4</sup>

The study did not generate objective measurements of sleep (as secondary outcomes) as many of the children refused to wear actigraph watches.<sup>2,3</sup> 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.<sup>7</sup> In the melatonin prolonged-release (Slenyto<sup>®</sup>) study, changes in social functioning and behaviour at home and school, measured using CGAS and 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.<sup>2</sup>

The main study included only four patients (3.2%) with neurogenetic disorders (all four patients had Smith-Magenis syndrome) and provides limited data in children with these conditions. However, the EMA review noted evidence from studies of other melatonin preparations in neurogenetic disorders.<sup>2,3</sup> 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.<sup>2</sup>

There are no direct comparative data relative to melatonin preparations used in Scottish practice.

The Bucher indirect comparison of melatonin prolonged-release (Slenyto<sup>®</sup>) tablets versus melatonin immediate-release capsules was limited by heterogeneity across the melatonin

prolonged-release (Slenyto®) study and MENDS study in baseline demographics, in particular, the proportion of children with autism (97% versus 40%) and the proportion of patients with only sleep maintenance problems (<4% versus 18%) which is a concern as both the immediate- and prolonged-release preparations appear to have little effect on sleep maintenance. Differences were also noted in melatonin dose range (2mg to 5mg versus 0.5mg to 12mg), design of the dose titration phase and discontinuation rates. It is unclear whether the observed increase in total sleep time associated with the prolonged-release formulation when compared with the immediate release capsules, would constitute a clinically meaningful difference. In addition, the 95% confidence intervals around the observed difference were wide making it difficult to draw conclusions.<sup>2,3,5</sup>

## Summary of comparative health economic evidence

The company submitted a cost-utility analysis which compared melatonin prolonged-release (Slenyto®) tablets with a weighted comparator of both prolonged-release (Circadin®) and immediate release melatonin. Clinical expert responses suggest that both Circadin® and Pharma Nord Syncrocin® (melatonin 3mg tablets) may be displaced.

A Markov cohort model separated patients into two cohorts, for melatonin prolonged-release (Slenyto®) and the weighted comparator (melatonin prolonged-release [Circadin®] or IR melatonin). Patients receiving prolonged-release melatonin [Circadin®] were further subdivided into those receiving whole tablets (receiving the benefits of prolonged-release melatonin) and crushed tablets (receiving the benefits of immediate-release melatonin). Beyond treatment allocations, all patients entered the model in the “on treatment” health state and could transition to the absorbing “discontinued” state. Patients remained on treatment until they transitioned to the absorbing state, where they were assumed to receive no further treatment. A time horizon of 10.3 years was used, representing the duration from the mean age of participants in the melatonin prolonged-release (Slenyto®) clinical study to the maximum age of eligibility for treatment (18 years).

Clinical data for the economic evaluation were obtained from the main study of melatonin prolonged-release (Slenyto®) in this indication, as well as an indirect comparison with an unpublished subgroup of the MENDS study as described above.<sup>3,5</sup> Transition probabilities were derived from treatment discontinuation rates observed within the two trials, based on a naïve unadjusted comparison. Discontinuation rates for melatonin prolonged-release (Slenyto®) were extrapolated across the time horizon based on the proportion of patients on treatment at weeks 14 and week 103 of the clinical study; discontinuation rates for melatonin immediate-release were extrapolated separately based on a single estimate at 12 weeks of follow-up. No alternative approaches were provided in the submission from the company but were subsequently provided as additional analyses.

The company conducted a multi-stage mapping exercise to translate condition-specific patient and caregiver-reported outcomes into utility estimates for IR melatonin. Due to the paucity of utility data relevant to this indication, no estimates of baseline utility were available. A treatment effect

was applied to derive melatonin prolonged-release utilities from the MENDS study, based on the estimated relative improvement in total sleep time over melatonin immediate-release derived from the Bucher ITC. Total sleep time at subsequent milestones from the uncontrolled extension study were then used to adjust this utility increment further by assuming ongoing improvements for prolonged-release melatonin would not be observed for IR melatonin. The utility estimates were 0.0357 for patients receiving IR melatonin, 0.0094 for discontinued patients and were 0.0405 (weeks 1 – 13), 0.054 (weeks 14 – 25), 0.068 (weeks 26 – 38) and 0.064 (weeks 39 onwards) for prolonged-release melatonin.

The costs of medicine acquisition were included for both melatonin prolonged-release (Slenyto® and Circadin®) and a weighted average of IR melatonin based on the use of both prescription-level data from Public Health Scotland from Oct 2019 – May 2020, and UK data regarding the proportion of patients aged 2 – 18 receiving different formulations. Approximately two-thirds of IR melatonin dispensed was assumed to be as oral tablets, with the remainder as a higher-cost oral solution.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price.

Costs were applied on a ‘per mg’ cost of £0.26/mg (Circadin®) and £0.54/mg (blended IR melatonin) and £0.33 respectively. An alternative scenario investigating the use of IR melatonin (Syncrocin®; £0.17/mg) was provided upon request. The costs of adverse event management or best supportive care following discontinuation were assumed constant and were not included.

The base case results for melatonin prolonged-release (Slenyto®) versus melatonin immediate-release showed an incremental cost-effectiveness ratio (ICER) of £20,217.

**Table 3: Key scenario analyses**

#	Scenario	ICER
1.	Time horizon of 16 years (reflecting treatment from 2 – 18 years)	£21,165
2.	Pairwise comparison: Circadin®	£45,174
3.	Pairwise comparison: blended IR melatonin comparator	£2,965
4.	Pairwise comparison: melatonin 3mg (£0.17/mg)	£29,728
5.	Correction of Slenyto® and IR melatonin discontinuation rates (using intent-to-treat data)	£23,632
6.	Application of Bucher method (relative improvement in TST) to derive IR melatonin discontinuation	£10,584
7.	Constant utility increment for Slenyto® (no additional utility gain beyond week 13)	£53,900
8.	Slenyto® utility equal to IR melatonin	£83,841
9.	Original base case including caregiver disutility (full utility increment for prolonged-release melatonin)	£10,733
10.	Scenario 7 including caregiver disutility (reduced utility increment for prolonged-release melatonin)	£28,613
11.	Scenario 8 including caregiver disutility (no utility increment for prolonged-release melatonin)	£44,508

12.	Combined analysis, Circadin® comparison, patient only (Scenarios 1, 2, 5, 7)	£162,563
13.	Combined analysis, Circadin® comparison, patient and caregiver (Scenarios 1, 2, 5, 10)	£86,299
14.	Combined analysis, IR melatonin comparison, patient only (Scenarios 1, 3, 5, 7)	£65,391
15.	Combined analysis, IR melatonin comparison, patient and caregiver (Scenarios 1, 3, 5, 10)	£34,714

With the exception of amendments to the cost inputs, the approach to estimating clinical effectiveness and utilities largely matched that of the original submission, despite important limitations being highlighted during the previous SMC assessment. The individual impact of these issues are described below, but overall this means the results of this analysis may lack face validity and potentially overestimate the relative benefit of prolonged-release melatonin (Slenyto®) versus standard practice.

- The use of a weighted comparator is non-standard and reduces the transparency of the results against the key displaced comparator (Circadin®). Additional scenarios were obtained, highlighting a higher ICER when comparing with Circadin® (Scenario 2). NDC felt that although a blend of comparators is likely to be representative of clinical practice, it is more likely to be an even split between Circadin® and IR melatonin tablets, with a minority (<10%) expected to receive melatonin in liquid form.
- The uncertainty associated with the double-mapping approach to estimating utilities was not adequately explored in the company submission, as it assumes each step in the process is the 'true' value. In addition, the approach relies on assumptions that both utilities increase linearly regardless of baseline total sleep time, and that a relative improvement in total sleep time will result in a proportionate increase in utility. These combined assumptions do not appear to align with relevant published literature which suggest a stabilisation of utility after reaching an optimal sleep duration.<sup>6,7</sup> More conservative estimates demonstrate substantial upwards sensitivity to the assumed utility increment associated with prolonged-release melatonin (Scenario 7 tests the assumption of a degree of assumed utility benefit, whilst Scenario 8 assumes the small improvement in TST does not translate into a utility benefit).
- The approach to estimating blended costs of IR melatonin requires a number of assumptions. Input from clinical experts suggests that the formulation of IR melatonin listed in the Scottish Drug Tariff (melatonin 3mg) may be most appropriate, and is associated with a significantly lower acquisition cost. This results in significantly higher ICERs than pairwise comparison with the blended comparator (Scenario 4). The cost of the oral solution is higher, although is not currently listed in the Scottish Drug Tariff.
- Although it is appropriate to consider caregiver disutility in this assessment, the approach to deriving utilities is subject to the same limitations as the derivation of patient utilities. The extent of caregiver utility benefit may therefore be overestimated. More conservative scenarios are shown in Scenario 10 (assuming a degree of benefit) and Scenario 11 (assuming the small improvement in TST does not translate into a utility benefit).

- The time horizon potentially does not reflect the corresponding assumptions regarding the proportions of patients who crush Circadin® tablets (which includes patients from 2 years and older) and a longer time horizon may be more appropriate. The use of a horizon covering the longest possible treatment duration (16 years) results in a slight increase in the ICER (Scenario 1).

Overall, these weaknesses are expected to have a significant impact on the results of the analysis. They appear to bias the results in favour of melatonin prolonged-release (Slenyto®), with the potential to overestimate the incremental QALY gain for the new intervention. The use of more conservative assumptions in combined scenario analyses results in significant upwards influence on the ICER (Scenarios 12 – 15). The most plausible ICER for a weighted comparator is likely to fall somewhere between the ICERs for the combined scenarios using pairwise comparison with Circadin, and pairwise comparison with IR melatonin. Due to the limitations outlined above, the economic case has not been demonstrated.

## Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from ADHD Parent Support West Glasgow and The Smith-Magenis Syndrome Foundation UK. ADHD Parent Support West Glasgow is an unincorporated organisation and The Smith-Magenis Syndrome Foundation UK is a registered charity.
- ADHD Parent Support West Glasgow has not received any pharmaceutical company funding in the past two years. The Smith-Magenis Syndrome Foundation UK has received 1.9% pharmaceutical company funding in the past two years, including from the submitting company.
- Getting to sleep and staying asleep is a significant issue for many children with Autistic Spectrum Disorder (ASD), while a child with Smith-Magenis Syndrome (SMS) has a different sleeping pattern to the rest of their family and community. The impact on affected children includes anxiety and distress at night, and has a serious impact on mood, cognition, concentration and learning during the day. For children with SMS, their activity whilst others are sleeping can increase the risk of serious incidents for both the child and their family. There is also a major impact on parents and siblings, including loss of sleep with the need to stay awake during the night to supervise an child who is up, and knock-on consequences of stress, anxiety, depression and difficulty functioning and working.

- Currently there is no licensed version of time-released melatonin for children. The only medicine which is available is melatonin prescribed off-label. A mini-tablet available in a higher strength would have advantages for children, especially for those with sensory issues.
- Having Slenyto available to families of children with ASD could make a difference to their quality of life. A slow release product may be more effective than melatonin which is currently available. Appropriate use of modified-released melatonin may extend the night time sleep period for children with SMS, with reduced early morning waking. Reducing the negative impact of night waking on family sleep may increase caregivers' capacity to more effectively provide support, which is eroded through chronic sleep disturbance.

### Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published Assessment, diagnosis and interventions for autism spectrum disorders (ASD): A national clinical guideline (SIGN 145) in June 2016.<sup>6</sup> This recommends a trial of melatonin to improve sleep should be considered in children with ASD who have sleep difficulties which have not resolved following behavioural interventions. Use of melatonin should follow consultation with a paediatrician or psychiatrist with expertise in the management of sleep medicines in children and/or ASD, and be in conjunction with behavioural interventions. Melatonin prescription should be reviewed regularly in the context of any emerging possible side-effects and/or reduced therapeutic effect. Prescribing of Circadin® for children is considered as off-label use and prescribing of any other melatonin products would be unlicensed use.

The National Institute of Health and Care Excellence (NICE) published clinical guideline number 170, Autism spectrum disorder in under 19s: support and management, in August 2013 and this was reviewed in September 2016. For children or young people with autism who develop a sleep disorder this recommends that pharmacological interventions to aid sleep are not used unless sleep problems persist despite following the sleep plan and they are having a negative impact on the child or young person and their family or carers. If a pharmacological intervention is used to aid sleep it should only be used following consultation with a specialist paediatrician or psychiatrist with expertise in the management of autism or paediatric sleep medicine. It should be used in conjunction with non-pharmacological interventions and be regularly reviewed to evaluate the ongoing need for a pharmacological intervention and to ensure that the benefits continue to outweigh the side effects and risks.<sup>7</sup>

### Additional information: comparators

Off-label use of melatonin immediate-release tablets and solution and modified-release tablets.

### Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
<b>Melatonin prolonged-release (Slenyto®) tablet</b>	<b>2mg to 10mg daily</b>	<b>500 to 2,500</b>

*Costs from eVadis on 5 October 2020. Costs do not take patient access schemes into consideration.*

### Additional information: budget impact

The submitting company estimated there would be 1,945 new patients eligible for treatment with melatonin prolonged-release (Slenyto®) in year 1, reducing to 1,936 new patients eligible for treatment in year 5. An estimated uptake of 100% (1,945 patients) from year 1 was assumed.

At list prices, the impact on the medicines budget was estimated at £2.6m in years 1 to 5. The net medicines budget impact was estimated £1.1m in years 1 to 5.

The net budget impact estimates are dependent on the relative proportion of comparators used and may vary depending on local prescribing patterns.

[Other data were also assessed but remain confidential.\\*](#)

## References

1. Flynn Pharma Ltd. Melatonin prolonged-release (Slenyto®). Summary of product characteristics. Electronic Medicines Compendium [www.medicines.org.uk](http://www.medicines.org.uk) Last updated 8 June 2020.
2. European Medicines Agency (EMA). European public assessment report. Melatonin prolonged-release (Slenyto). 26 July 2018, EMA/556280/2018 [www.ema.europa.eu](http://www.ema.europa.eu)
3. Gringras P, Nir T, Breddy, J, et al. Efficacy and safety of pediatric prolonged-release melatonin for insomnia in children with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry 2017; 56: 948-57.
4. Maras A, Schroder CM, Malow BA, et al. Long-Term Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children with Autism Spectrum Disorder. J Child Adolesc Psychopharmacology 2018; 28: 699-710.
5. Gringras P, Gamble C, Jones AP, et al. Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. Br Med J 2012; 345: e6664.
6. Scottish Intercollegiate Guidelines Network. Assessment, diagnosis and interventions for autism spectrum disorders (ASD): A national clinical guideline (SIGN 145) 2016. Available at <https://www.sign.ac.uk/assets/sign145.pdf> (Accessed 02/10/2020).
7. European Medicines Agency (EMA). Guideline on medicinal products for the treatment of insomnia, EMA/CHMP/16274/2009 previously (EMEA/16274/2009) Rev. 1, 17 February 2011.

This assessment is based on data submitted by the applicant company up to and including 13 November 2020.

*\*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: [http://www.scottishmedicines.org.uk/About\\_SMC/Policy](http://www.scottishmedicines.org.uk/About_SMC/Policy)*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a

patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*