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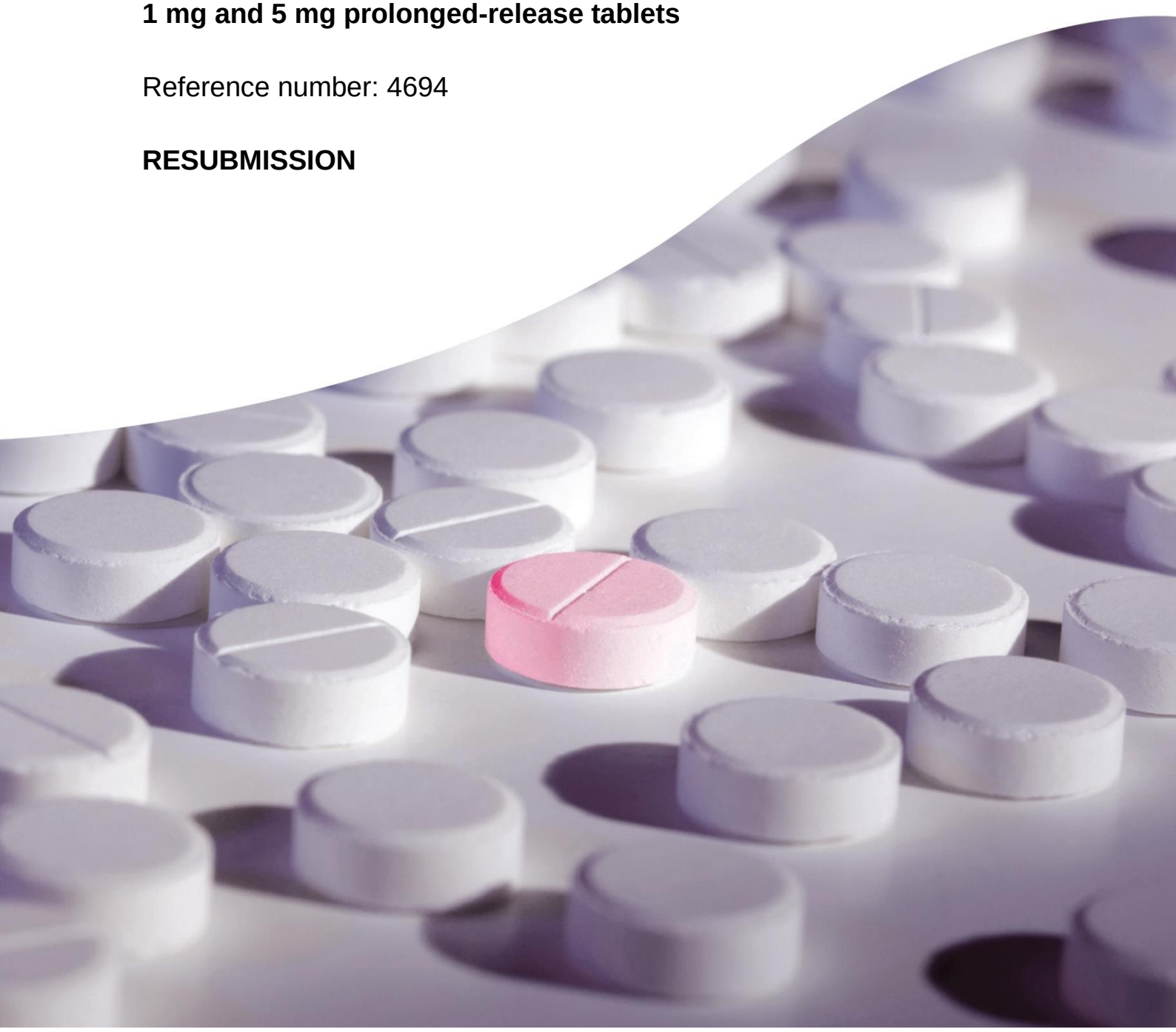
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

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

Reference number: 4694

RESUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

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AWMSG Secretariat Assessment Report
Melatonin (Slenyto®) 1 mg and 5 mg prolonged-release tablets

1.0 KEY FACTS

Assessment details	Melatonin (Slenyto®) for the 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. This is a resubmission for Slenyto® with a Wales Patient Access Scheme (WPAS) and the inclusion of Circadin® as a comparator in the cost-effectiveness model. AWMSG previously appraised Slenyto® for this indication and issued a non-recommendation in November 2019 because the case for cost-effectiveness was not proven.
Current clinical practice	There are no other licensed medicines for the above indication in the UK. The main treatments available are non-pharmacological, including good sleep hygiene measures; adjunctive medicines are often prescribed off-label. In Wales these include prolonged- and immediate-release melatonin.
Clinical effectiveness	There are no efficacy or safety studies comparing Slenyto® with other melatonin products. The company's submission includes a phase III study designed to evaluate the safety and efficacy of Slenyto® versus placebo in children with autism spectrum disorder or neurogenetic disorders, whose insomnia had not improved after standard behavioural interventions. Treatment with Slenyto® resulted in a statistically significant improvement in total sleep time compared with placebo, which was associated with improved externalising behaviour in children and caregivers' wellbeing.
Cost-effectiveness	A cost-utility analysis compares Slenyto® 1 mg and 5 mg tablets with a comparator bundle of Circadin® 2 mg and immediate-release melatonin for the 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. The company base case suggests an incremental cost-effectiveness ratio of [commercial in confidence figure removed] per quality-adjusted life-year gained. AWTTC considers the most plausible incremental cost-effectiveness ratio to be higher than the company's base case. Using the model submitted, application of more plausible assumptions reflecting AWTTC-sought clinical expert opinion results in incremental cost-effectiveness ratios ranging between [commercial in confidence figure removed] and [commercial in confidence figure removed] per quality-adjusted

	life-year gained, if the base case market share for Circadin® is considered appropriate. However, the model is characterised by significant uncertainty and the potential for bias, particularly in utility estimates, including those scenarios considered most plausible by AWTTC.
Budget impact	The company estimates that 1,323 patients are likely to receive treatment with Slenyto® in Wales in Year 1, increasing to 1,348 patients in Year 5. The company base case suggests a saving of [commercial in confidence figure removed] in Year 1, increasing to a saving of [commercial in confidence figure removed] in Year 5. However, there is uncertainty around the prevalence estimates, dosing, and unit costs for the immediate-release comparator bundle. AWTTC estimates that there will be additional costs rather than cost savings, ranging between [commercial in confidence figure removed] and [commercial in confidence figure removed], if the base case market share for Circadin® is considered appropriate.
Additional factors to consider	Slenyto® is the first licensed medicine for the indication under consideration where off-label or unlicensed medicines are often used.

This assessment report is based on evidence submitted by Flynn Pharma Ltd[1] and an evidence search conducted by AWTTC on 6 October 2020.

2.0 BACKGROUND

2.1 Condition and clinical practice

The European Medicines Agency (EMA) states that the prevalence of insomnia is as high as 50% to 75% in children with neurodevelopmental disorders[2]. This group of children includes those with autism spectrum disorder (ASD) and Smith-Magenis syndrome (SMS: a rare genetic disorder involving mild-to-severe learning disability[3] and extremely severe sleep disorder[2]). There is some evidence that indicates these children might have low endogenous melatonin secretion and abnormal circadian rhythmicity, which might explain the abnormal sleep-wake cycles[2]. Common sleep problems include difficulties initiating and maintaining sleep, short night sleep duration, early morning waking, and daytime sleepiness[4]. These sleep disturbances have a major impact on children and might exacerbate externalising and internalising behaviours, such as aggression, activity level, emotional reactivity, and anxiety. Caregivers of children with sleep problems are also at greater risk of sleep deprivation, leading to stress and impaired mental health[4].

The National Institute for Health and Care Excellence (NICE) guideline on the management of ASD in under 19s recommends sleep hygiene interventions before escalating to adjunctive pharmacological treatment of sleep disturbances in children[5]. For children and adolescents needing pharmacological therapy, off-label or unlicensed melatonin preparations are often prescribed. Circadin® 2 mg prolonged-release (PR) tablet is a melatonin preparation licensed for the short-term treatment of primary

insomnia characterised by poor quality of sleep only in adults aged 55 years or older[6]. Circadin® is well established as current first-line treatment in Wales for the treatment of insomnia in children and adolescents with ASD and/or SMS, where sleep hygiene measures have been insufficient; second line treatment is usually melatonin oral solution.

In 2019, melatonin 1 mg/1 ml oral solution and melatonin 3 mg tablets were licensed for the short-term treatment of jet-lag in adults[7,8]. Their Summaries of Product Characteristics state that they should not be used in children and adolescents because of safety and efficacy concerns[7,8].

2.2 Medicine

Melatonin is a naturally occurring hormone produced by the pineal gland in the brain[9]. It is involved in co-ordinating the body's sleep-wake cycle and helping to regulate sleep[9]. Slenyto® acts at the melatonin receptors (MT1, MT2) which are involved in the regulation of circadian rhythms and sleep[10]. Slenyto® is the first licensed medicine for the indication under consideration.

Slenyto® was granted marketing authorisation by the EMA in September 2018, and is formulated as a 1 mg, or 5 mg, film-coated tablet for once-daily administration. It was specifically developed for children: at 3 mm in diameter it is easier to swallow and is small enough to put into food such as yoghurt, orange juice or ice-cream[2]. The recommended starting dose of Slenyto® is 2 mg once daily, with a maximum dose of 10 mg[10,11]. The applicant company anticipates that Slenyto® will be used in place of off-label Circadin® and unlicensed immediate release (IR) melatonin preparations[1].

The All Wales Medicines Strategy Group (AWMSG) has previously appraised Slenyto® for this indication and issued a non-recommendation in November 2019 because the case for cost-effectiveness was not proven[12]. A resubmission has been provided with a revised cost-effectiveness model using a new comparator, updated trial data and a Wales Patient Access Scheme (WPAS)[1].

2.3 Comparators

The comparators included in the company's submission are:

- unlicensed IR melatonin tablets, capsules and oral solution[1]
- Circadin® 2 mg PR tablets[6].

2.4 Guidance and related advice

- NICE guideline (NG87). Attention deficit hyperactivity disorder: diagnosis and management (2018)[13]
- In NHS Wales, some health boards have shared care agreements for melatonin use in children and adolescents with sleep onset difficulties[14,15]
- NICE clinical guideline (CG170). Autism spectrum disorder in under 19s: support and management (2013)[5]
- NICE evidence summary (ESUOM2). Sleep disorders in children and young people with attention deficit hyperactivity disorder: melatonin (2013)[9]

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, melatonin (Slenyto®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation. A shared care agreement for prescribing may be considered.

3.0 CLINICAL EFFECTIVENESS

The company's submission included results from a pivotal, phase III, 13-week study (NCT01906866), which compared the efficacy and safety of Slenyto® with placebo in children with ASD or neurogenetic disorders who had not shown improvement in insomnia after standard behavioural interventions[16]. It also included results from an open-label follow-on study, in which all participants in the phase III pivotal study received Slenyto® at the 2 mg, 5 mg or 10 mg dose[17,18]. Because the company used IR melatonin as a comparator, their submission also included a study (MENDS) assessing the effectiveness and safety of IR melatonin in treating severe sleep problems in children with neurodevelopmental disorders[19]. Data from this study were used to inform the cost-effectiveness model.

3.1 NCT01906866

This was a randomised, double-blind, placebo-controlled, parallel-group, multicentre (Europe and USA) study[16]. To be included in the study, children needed to have impaired sleep for a minimum of three months, defined as: six hours or less of continuous sleep, and/or 30 minutes or more of sleep latency (the time taken to fall asleep) on three out of five nights. A total of 125 children and adolescents aged 2 to 17.5 years (97% with ASD and 3% with SMS), whose sleep failed to improve on behavioural intervention alone, were randomised in a 1:1 ratio to receive Slenyto® or placebo for 13 weeks[16]. Of these children, 35.2% (n = 44) were aged 2 years to 6 years[1].

All participants received 2 mg Slenyto® or placebo during the first three weeks of study treatment[16]. Thereafter, the dose could be increased to 5 mg if the patients did not improve from baseline by at least one hour in sleep latency, and/or total sleep time. Compliance was close to 100%, without the need to crush or dissolve the tablets[16].

The primary efficacy endpoint was the change from baseline in mean total sleep time after 13 weeks of double-blind treatment[16]. Total sleep time was assessed using the validated caregivers' Sleep and Nap Diary and was completed every morning by the parent or caregiver. The adjusted mean treatment difference for Slenyto® versus placebo was 32.43 minutes, which was statistically significant (Table 1). The efficacy of Slenyto® in all age subgroups was similar[16].

The secondary endpoint, sleep latency, was statistically significantly decreased with Slenyto® versus placebo[16]. There were no differences between Slenyto® and placebo for the other secondary endpoints assessed using the Sleep and Nap Diary, including: the longest sleep episode (the longest uninterrupted period of sleep after falling asleep) (Table 1); number of awakenings per night ($p = 0.474$) and duration of wake time ($p = 0.981$)[16].

At 13 weeks, no statistically significant differences were found for assessment scales measuring sleep disturbance in children (Composite Sleep Disturbance Index: see Glossary), daytime behaviour of children (Children's Global Assessment Scale and Strength and Difficulties Questionnaire: see Glossary), except for the subdomain "externalising behaviours" of the Strength and Difficulties Questionnaire (behaviours that are directed towards the external environment, such as hyperactivity-impulsivity, or aggression), for which melatonin showed a significant effect (Table 1)[16,20].

The exploratory efficacy endpoint consisted of three assessment scales to capture the effects on parents and caregivers. Caregivers' wellbeing, as assessed by the WHO-5 wellbeing questionnaire (see Glossary), showed a significant improvement[2,20]. There were no statistically significant differences documented for caregivers' daytime sleepiness or caregivers' quality of sleep at night, which were assessed by the Epworth

Sleepiness Scale (see Glossary), and Pittsburgh Sleep Quality Index scores (see Glossary), respectively (see Table 1)[2,20].

Table 1. Selected endpoints of NCT01906866[16,20,21]

Slenyto® versus placebo after 13 weeks of double-blind treatment (MMRM analysis)					
Endpoint	**n (Slenyto®)**	**n (placebo)**	**Estimated treatment difference (SE)**	**95% CI**	**p value**
Total sleep time* (minutes)	52	48	32.43 (15.11)	2.48 to 62.38	0.034
SL† (minutes)	52	48	−25.30 (9.79)	−44.71 to −5.90	0.011
LSE§ (minutes)	58	61	42.16 (21.44)	−0.42 to 84.73	0.052
CSDI§	55	48	−0.92 (0.511)	−1.93 to 0.09	0.074
"Externalising behaviours" subdomain of SDQ§	54	49	−0.83 (0.355)	−1.54 to −0.13	0.021
Caregivers' daytime sleepiness (ESS)¶	58	61	−1.29 (0.752)	−2.78 to 0.20	0.089
Caregivers' wellbeing (WHO-5)¶	58	61	2.17 (0.831)	0.53 to 3.82	0.01
Caregivers' quality of sleep at night (PSQI)¶	58	61	−0.81 (0.582)	−1.97 to 0.34	0.166

* Primary endpoint
† First secondary endpoint
§ Secondary endpoint
¶ Exploratory endpoint
CI: confidence interval; CSDI: Composite Sleep Disturbance Index; ESS: Epworth Sleepiness Scale; LSE: longest sleep episode; MMRM: mixed-effect model for repeated measure; n = number of participants with data; PSQI: Pittsburgh Sleep Quality Index; SDQ: Strength and Difficulties Questionnaire; SE: standard error; SL: sleep latency; WHO: World Health Organization

3.2 Open-label extension study

Study NCT01906866 was followed by an open-label, long-term follow-up phase for 91 weeks, in which subjects received Slenyto®[18]. Children who had received placebo during the 13-week study crossed over to receive Slenyto® in the extension study. After 13 weeks of the open-label phase, subjects could have an optional dose adjustment (i.e. children received either 2, 5 or 10 mg per day)[18].

After 39 weeks of follow-up in the open label phase (n = 80), total sleep time, sleep latency, longest sleep episode, number of awakenings, sleep quality and sleep disturbance were statistically improved versus the baseline scores irrespective of initial randomisation assignment[17]. After 39 weeks, 76% of patients achieved an overall improvement of one hour or more in total sleep time, sleep latency or both over baseline[17]. These endpoints have not been assessed after 91-week follow up.

Child sleep disturbance, caregivers' satisfaction of their child's sleep patterns, caregivers' quality of life and quality of sleep were significantly improved at the end of the 39-week follow-up compared with baseline[17]. These improvements were maintained through to the end of the 91-week follow-up (n = 74)[18].

3.3 MENDS study

This was a 12-week randomised, placebo-controlled trial of IR melatonin for the treatment of sleep disturbances in children[19]. The study involved 146 children in England and Wales, aged 3 years to 15 years 8 months, who had a range of neurological and developmental disorders and a severe sleep problem that had not responded to a standardised sleep behaviour advice booklet. All children started with a 0.5 mg capsule, which was increased through 2 mg, 6 mg and 12 mg depending on their response to treatment[19].

The primary outcome was total sleep time after 12 weeks of double-blind treatment[19]. The mean difference in total sleep time between the two treatment groups, adjusting for baseline mean total sleep time, was 22.4 minutes (95% confidence interval: 0.5 to 44.3 minutes; $p < 0.05$) more in the melatonin group than placebo, but the confidence interval excluded the 60 minute value determined to be the minimum clinically relevant value. IR melatonin reduced sleep latency ($p < 0.001$), but sleep efficiency did not improve. Composite Sleep Disturbance Index and Epworth Sleepiness Scale scores improved with IR melatonin, but child behaviour, family impact and parent's perception of child's sleep quality did not significantly improve[19].

3.4 Safety information

There are no safety data directly comparing Slenyto® with off-label and unlicensed melatonin[2]. The long-term safety (up to 2 years) in the extension study, highlighted in section 3.2, is in line with the known post-marketing safety profile of Circadin®[2]. There were no serious treatment-related adverse events[16], with somnolence, fatigue, mood swings, headache, irritability, aggression and hangover being the most common adverse events[10,11].

The Committee for Medicinal Products for Human Use highlighted that safety data for Slenyto® are limited to two years, and uncertainties remain in relation to its long-term safety, specifically related to pubertal development[2]. The Committee for Medicinal Products for Human Use suggests that this could be achieved post-marketing through routine periodic safety update reports and a dedicated post-authorisation safety study[2].

3.5 AWTTC critique

- As part of their assessment for Slenyto®, the EMA noted there are no approved medicinal products indicated for hypnotic use in the paediatric population. This results in medicines being prescribed that have no proven record of safety and efficacy in children, or no determination of paediatric dosing[2]. Slenyto® is the only medicine licensed to treat insomnia in children and adolescents aged 2 to 18 years with ASD and/or SMS, if sleep hygiene measures have not worked.
- In the pivotal placebo-controlled study (NCT01906866) Slenyto® demonstrated a statistically significant improvement in total sleep time and the study met its primary endpoint. Clinical expert opinion sought by AWTTC indicates that off-label Circadin® is mainly used first line in children in Wales; second-line treatment is usually melatonin oral solution. There are no studies directly comparing the efficacy of Slenyto® with that of Circadin® or any other melatonin product. The company included a study assessing the efficacy and safety of IR melatonin compared with placebo (MENDS study), but did not provide any indirect comparison versus Slenyto®. Data from the MENDS study were used to inform the cost-effectiveness model.
- The WHO-5 caregivers' wellbeing scale, and the caregivers' quality of sleep at night (total Pittsburgh Sleep Quality Index) significantly improved versus baseline in a 91-week extension study[18]. The EMA considered the improved wellbeing of caregivers to be an important endpoint[2].

- Clinical experts indicate that for children who are unable to swallow or have difficulty in swallowing tablets, an oral solution or crushed tablets would be used. Slenyto® tablets are a third of the diameter of Circadin® (3 mm versus 8.1 mm) and are coated to mask taste and odour. They can also be disguised in food. The applicant company highlights that these tablets were developed to meet the needs of children with swallowing difficulties (due to young age) and sensitivities to touch, odour or taste (due to autistic core symptoms).
- In the pivotal study, treatment compliance was around 100%. Principal investigators reported that there was no need to crush the Slenyto® tablets and that children were able to swallow the tablets.
- Slenyto® is also available as a 5 mg tablet and may reduce the tablet burden for children on higher doses.

4.0 COST-EFFECTIVENESS

4.1 Context

The company's submission includes a cost-utility analysis (CUA) comparing oral administration of Slenyto® 1 mg and 5 mg (PR melatonin) with a comparator bundle of Circadin® and various preparations of IR melatonin (including capsules, tablets and oral solution), for the treatment of insomnia in children and adolescents aged 2 to 18 years with ASD and/or SMS, where sleep hygiene measures have been insufficient (i.e. the full licensed indication).

The CUA takes the form of a Markov cohort model, comprising weekly cycles. The model adopts a 10.3 year time horizon and an NHS Wales/Personal and Social Services perspective. Costs and outcomes are discounted at 3.5%. The submission incorporates a Wales Patient Access Scheme (WPAS) discount for Slenyto®.

Patients enter the model and receive either Slenyto® or one of the medicines that make up the comparator bundle, which includes: Circadin® PR (intact tablets), Circadin® IR equivalent (crushed Circadin®) and IR melatonin. Patients can remain in these treatment states or transition to discontinuation - an absorbing state where it is assumed patients will receive no further pharmacological treatment. Patients are allocated to each of the comparator medicines through application of estimated market shares. These estimates are calculated based on published Prescription Cost Analysis (PCA) data for Wales[22] combined with English prescription data by age group[23]. It is thereby assumed that approximately 72% of patients in the comparator scenario are treated with Circadin®. It is further assumed that 32% of these patients will crush or quarter the tablet; effectively rendering it equivalent to IR melatonin[24]. The assumption for the proportion of patients who crush their tablets is supported by an unpublished study[25].

The data used to inform transition probabilities for Slenyto® are derived from the pivotal study and extension study for Slenyto®[16,17,21] (Slenyto® studies), and the MENDS study for IR melatonin[19]. Discontinuation rates for patients in the Circadin®-treated PR effect health state are assumed to be equal to those for patients in the Slenyto®-treated state and patients in the Circadin®-treated IR effect state are assumed to have the same discontinuation rates as patients in the IR melatonin-treated state. The Slenyto® studies captured patient discontinuation after 13 weeks and 103 weeks[16,17,21]. It is assumed that patients discontinue at a constant weekly rate over the first 13 weeks, and that this weekly rate decreases after Week 13, after which it remains constant[16]. The MENDS study captured discontinuation after 12 weeks of IR melatonin treatment only. A ratio for discontinuation (based on Week 12 and Week 13 data for IR melatonin and

Slenyto®, respectively) is applied to estimate the discontinuation rate from Week 13 onwards for IR melatonin, thereby applying an assumption of proportionality over time between the medicines. Discontinuation includes both protocol and non-protocol related discontinuations reported in the studies.

The model includes acquisition costs only. The base case uses mean dosing from the Slenyto® studies[16,17,21] and from the MENDS study for IR melatonin[19]. The observed mean daily dose of Slenyto® was recorded at three time points. The model assumes a 2 mg daily dose in Weeks 1 to 3, 3.77 mg dose in Weeks 4 to 26, and 5.33 mg dose from Week 27 onwards. In the MENDS study, dosing of IR melatonin was observed every week. The model assumes a 1.79 mg dose in Weeks 1 to 3, 6.41 mg in Weeks 4 to 13 and 6.49 mg from Week 14 onwards. The mean daily dose of Circadin® (both IR and PR) is assumed to be equal to that of Slenyto®. Slenyto® acquisition costs are based on a WPAS discount price. Circadin® acquisition unit costs are sourced from the BNF[26]. IR melatonin acquisition costs have been derived from analysis of prescribing data in Wales and GPrX data for all formulations of IR melatonin[22,27]. This average price per mg is calculated by dividing the total cost of all IR melatonin products prescribed to children in Wales (June 2020) by the total mg of all these products. No costs are accrued in the discontinuation state. The model also does not capture costs associated with treatment-related adverse events.

Health outcomes are accrued in each of the states (including the discontinuation state). The pivotal studies for Slenyto® and IR melatonin collected data on total sleep time, and the MENDS study[19] also collected data on the family impact module of the paediatric quality of life inventory (PedsQL). However, data were not collected in the pivotal studies for generic preference-based health-related quality of life. Furthermore, a systematic literature review did not uncover child utility values that could be directly used in the model. The company therefore conducted a secondary systematic literature review to inform an indirect transformation. This involved converting the family impact score of the paediatric quality of life inventory outcome collected in the MENDS study[19] (which assesses the quality of life of the caregiver) to child (and caregiver, in the scenario analyses) utility estimates for both the IR melatonin-treated and Slenyto®-treated health states. This process was informed by two papers[28,29] and required application of an assumption of linearity when mapping changes in the Children's Sleep Habits Questionnaire (CSHQ), to changes in paediatric quality of life inventory outcome, and subsequently transforming these into utility changes for both the Health Utilities Index (HUI-3) and EQ-5D to estimate impact on caregiver utility in the scenario analyses. It is also assumed that differences in effectiveness between Slenyto® and IR melatonin in terms of utility are proportional to the difference in effectiveness in terms of total sleep time. The company assumes a constant utility value, linked with the data collected at 12 weeks, for IR melatonin. In contrast, given the multiple data collection points in the pivotal study, the utility associated with Slenyto® treatment predominantly increases in the first year, after which it is assumed to remain constant. Health outcomes from the placebo arm of the Slenyto® pivotal study are applied to patients in the discontinued state[16]. The model does not capture disutility associated with treatment-related adverse events.

One-way deterministic and probabilistic sensitivity analyses test the influence of the uncertainty of individual parameters on the model results. The parameters tested, among others, include: Circadin® market share, acquisition costs, mean daily dosing, weekly utility values and discontinuation rates. The scenario analyses also explore the effects of: including both child and caregiver utility in the model, and an alternative assumption for the percentage of patients who crush or quarter Circadin®.

4.2 Results

The results of the company's base case are detailed in Table 2. When compared with a bundle comprising Circadin® and IR melatonin, the incremental cost-effectiveness ratio (ICER) generated is [commercial in confidence figure removed] per quality-adjusted life-year (QALY) gained. The cost differences can be attributed entirely to differences in treatment acquisition costs. The incremental QALY gains are predominantly driven by the assumed increasing utility differences over time between the treatments.

Table 2. Results of the base case analysis

	Slenyto®	Comparator bundle		Difference
		Circadin®	IR melatonin	
Total costs	¶¶	**£6,347,649**		¶¶
		£2,416,127	**£3,931,522**	
Total QALYs	**492.60**	**384.14**		**108.46**
		305.32	**78.82**	
ICER (£/QALY gained)	¶¶			

ICER: incremental cost-effectiveness ratio; IR: immediate release; QALY: quality-adjusted life-year
Numbers may not compute due to rounding.
¶¶ commercial in confidence figure removed

The results of the univariate sensitivity analysis reveal that the ICER is most sensitive to the assumed market share for Circadin®, Slenyto® cost per mg, dosing of Slenyto® and Circadin® from Week 27 onwards, IR melatonin cost per mg, IR melatonin daily dosing from Week 27 onwards, the discontinuation rates of both medicines (particularly the rates applied at Weeks 12 and 13), and utility values from 52 weeks onwards for Slenyto® and Circadin® PR, and all weeks for IR melatonin and Circadin® IR. The univariate analyses exploring market share for Circadin® at its upper 95% confidence interval boundary generated an ICER of [commercial in confidence figure removed]. All other one-way analyses conducted generated ICERs lower than [commercial in confidence figure removed] per QALY gained. The results of the scenario analyses are assessed in terms of plausibility in Table 3.

Probabilistic sensitivity analyses suggest that Slenyto® has an 88.20% and 96.16% probability of being cost-effective at a threshold of £20,000 and £30,000 per QALY gained, respectively.

Table 3. Results of scenario and sensitivity analyses

Scenarios/sensitivity analyses	ICER (£/QALY gained)	Plausibility
Scenario 1 Alternative unit cost for IR bundle (79 p/mg)	¶¶	The IR melatonin bundle used in the base case includes liquid preparations, tablets and capsules. Clinical experts in Wales report that this patient group is prescribed either Circadin® or a liquid preparation, in accordance with care protocols. Welsh prescribing data reveal a blended unit cost for IR melatonin liquids of 79p, which is lower than the blended unit cost for IR melatonin used in the base case, and lower than the blended unit cost for IR melatonin liquids included in requested sensitivity analyses. AWTTC was unable to replicate the blended unit cost for IR melatonin liquids used in the company-submitted analyses using Welsh prescribing data unit costs sourced by AWTTC. This scenario provides a useful insight into the impact on the ICER if the IR melatonin bundle includes liquid preparations only.
Scenario 2 Alternative dosing regimens - informed by BNFC a) 2 mg Slenyto, 2 mg IR bundle b) 10 mg Slenyto, 10 mg IR bundle c) 5 mg Slenyto, 5 mg IR bundle	**a)** ¶¶ **b)** ¶¶ **c)** ¶¶	Normally, it would be recommended that both dose and effect reflect the pivotal studies. However, given the uncertainties in the utility estimates and the naïve approach to comparisons of efficacy, there is uncertainty in the comparative relationship between these in this instance. Given this and AWTTC clinical expert opinion relating to comparative efficacy, an exploration of alternative dosing informed by BNFC dosing recommendations provides a useful alternative scenario for consideration. However, these scenarios notably include the higher unit cost for the IR melatonin bundle. If the 5 mg scenario is updated to include a unit cost of 79p, this increases the ICER further to [commercial in confidence figure removed].
Scenario 3 Company base case with inclusion of caregiver utility in addition to child utility in model	¶¶	A useful analysis which has plausibility as a scenario analysis; facilitating an evaluation of the wider effects on health-related quality of life for the patient's family. This inclusion has the effect of almost doubling incremental utility.
Scenario 4 Alternative assumption for the percentage of patients who crush/quarter Circadin® - 50% of patients	¶¶	It is assumed that the act of crushing Circadin® removes its prolonged release properties and produces the same clinical characteristics as IR melatonin. The utility and discontinuation profile of crushed Circadin® is assumed equal to IR melatonin. There is supporting evidence to suggest that if quartered or crushed, the release profile of Circadin® becomes more like that of an IR preparation[24]. However, the methods used to estimate utility and discontinuation for IR melatonin are subject to notable uncertainty.
ICER: incremental cost-effectiveness ratio; IR: immediate release; QALY: quality-adjusted life year ¶¶ commercial in confidence figure removed		

4.3 AWTTC critique

The submission provides a detailed, transparent account of the methods, assumptions and data sources used in the analysis. However, the methods of comparison, and a number of the assumptions applied introduce uncertainty and the potential for bias.

Strengths and limitations:

- The company assumes market shares based on prescribing data. The ICER is most sensitive to this parameter. If the market share is underestimated for Circadin®, this biases the analysis in favour of Slenyto®. Conversely, if it overestimates, it biases against Slenyto®.
- The validity of comparative efficacy inputs is questionable in all scenarios, given the heterogeneity between patient populations in the pivotal studies, and the methods applied (i.e. naive unadjusted comparison).
- The transformation process used to derive utility values introduces further notable uncertainty. Unadjusted changes in paediatric quality-of-life inventory outcome scores from the MENDS study[19] have been used to inform IR melatonin utility gains, which have also been applied to Circadin® IR. For Slenyto® and Circadin® utility estimates are based on the ratio of total sleep time from the Slenyto® pivotal study, extension study and MENDS study[16,17,19]. The assumption of linear proportionality applied to transformation calculations has the potential to introduce estimate bias.
- The transformation process appears to use two different measures for PedsQL. The Delahey et al. study[28] collected PedsQL data using a 23-item questionnaire[30]; and this is what the utility conversion is based upon (−0.65 decrease in total PedsQL score for each 1 point increase in CHSQ score). However, the MENDS study[19] used a 36-item Family Impact module of the PedsQL questionnaire[31]. It is questionable whether it is appropriate to apply the relationship between CHSQ and PedsQL 23 item questionnaire, to the 36-item Family Impact Module of the PedsQL. This adds further uncertainty to the utility estimates used in the model.
- The utility estimates suggest increasing utility gains associated with Slenyto® and Circadin® PR over time, and lower constant gains for IR melatonin and Circadin® IR. The company rationalises the asymmetric modelling of utilities on the basis that in the MENDS study[19], all patients could escalate to the maximum dose capsules (12 mg) throughout the 12 weeks of the study, thereby facilitating measurement of the full effectiveness of IR melatonin within that period of time. In contrast, patients in the Slenyto® pivotal trial received slower up-titration. However, the modelled superiority of Slenyto® is not supported by AWTTC-sought clinical expert opinion.
- There is notable uncertainty around the representativeness of the IR melatonin bundle for this patient group in Wales. There is considerable variability in the unit costs of these preparations, and the potential for bias if those included are not reflective of current Welsh prescribing practices. AWTTC-sought clinical expert opinion suggests that this patient group is prescribed either Circadin® or liquid melatonin, in accordance with local care protocols. If the unit cost of the IR melatonin bundle is adjusted to reflect Welsh prescribing data for liquid preparations only (i.e. excluding IR melatonin tablets and capsules), this increases the ICER to [commercial in confidence figure removed] per QALY gained.
- The dosing used in the model is predominantly reflective of those used in the pivotal studies. However, the higher dosing applied for IR melatonin may not be reflective of current practices. Local shared care protocols reflect BNFC dosing recommendations, irrespective of whether melatonin is IR or PR[14,15]. The BNFC for Slenyto® recommends initiating a daily dose of 2 mg, increasing if necessary

to 5 mg daily, or a maximum of 10 mg[32]. The BNFC for melatonin PR suggests an initial daily dose of 2 mg, increasing to 4–6 mg if necessary, or a maximum of 10 mg[32]. If the higher dosing for IR melatonin is not reflective of current practice, this will bias the results in favour of Slenyto®. Upon request the company submitted additional scenario analyses to explore the effects of alternative dosing assumptions (see Table 3).

- The efficacy equivalence applied in the model for Circadin® is an assumption, attributed to a lack of studies for this off-label patient population. This approach inherently introduces uncertainty and the potential for bias.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC did not identify any studies relevant to the cost-effectiveness of Slenyto® versus IR melatonin or Circadin® in the treatment of patients with insomnia in the patient population of interest.

5.0 BUDGET IMPACT

5.1 Context and methods

The company estimates that there are 1,323 paediatric patients aged 2 to 18 years with ASD in Year 1 who require pharmacological therapy for insomnia. This estimate has been derived using data from England to identify the proportion of the paediatric population prescribed melatonin[27,33] and findings from a survey on the prescribing of melatonin in children and adolescents, conducted over a one-month period in 2016 in one London borough, to identify what proportion of these patients are likely to have ASD[34]. This proportion is then applied to Welsh Government age-based population statistics[35] to produce estimates for Wales. Mortality in this patient population is assumed to be identical to the general population mortality rate for this age group, which is effectively captured in Welsh population data. The Slenyto® studies and MENDS study have been used to inform discontinuation estimates[16,17,19].

A market share of 100% per annum is applied to estimate the number of people likely to be prescribed Slenyto® in Wales for the indication covered in the submission. The model assumes a mean daily dose of 5.33 mg for Slenyto® and Circadin®, and a mean daily dose of 6.49 mg for the IR melatonin bundle. A WPAS price is used to inform medicine acquisition costs for Slenyto®. Medicine acquisition costs for the IR melatonin bundle and Circadin® bundle are taken from Welsh prescribing data[22]. Sensitivity and scenario analyses explore the impact of alternative market share assumptions, where Slenyto® only displaces the assumed Circadin® market share or only replaces the assumed market share for IR melatonin. AWTTC requested further analyses to explore the effects of alternative assumptions for comparative dosing and IR bundle cost.

5.2 Results

The budget impact is presented in Table 4. The company estimates that introducing Slenyto® would lead to an overall saving of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. This estimate incorporates cost differences resulting from the displacement of Circadin® and a bundle of IR melatonin medicines currently dispensed in Wales, which includes tablets, capsules and oral solution.

The company carried out a sensitivity analysis to explore the effects of reducing the estimate for the uptake of Slenyto®. If Slenyto® is assumed to replace the market share for Circadin® only; this resulted in a budget impact of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5.

If Slenyto® is assumed to only displace IR melatonin this results in savings projections of [commercial in confidence figure removed] in Year 1 increasing to [commercial in confidence figure removed] in Year 5. The predicted budget impact is therefore highly sensitive to displacement assumptions.

Analyses were also conducted to explore alternative dosing assumptions and IR bundle cost. If an assumption of equal dosing of 5 mg for both Slenyto® and comparators is applied, this results in a budget impact of [commercial in confidence figures removed] in Years 1 and 5, respectively. However, these estimates include the higher IR bundle unit cost. If this scenario is adjusted to include an IR melatonin unit cost of 79p, this results in a budget impact of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5.

Table 4. Company-reported costs associated with use of Slenyto® for the treatment of insomnia in the populations of interest

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (indication under consideration)	1,323	1,331	1,338	1,344	1,348
Uptake of new medicine (%)	100%	100%	100%	100%	100%
Number of patients receiving new medicine allowing for discontinuations	1,144	1,151	1,157	1,162	1,166
Medicine acquisition costs in a market without new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable	¶¶	¶¶	¶¶	¶¶	¶¶
Numbers might not compute due to rounding ¶¶ commercial in confidence figure removed					

The company has not explored net resource implications arising from the introduction of Slenyto®.

5.3 AWTTC critique

- The submission provides details of the methods and data sources used to estimate budget impact.
- The prevalence calculations provided in the base case for the proportion of children and adolescents prescribed melatonin who have ASD are based on age-related prescribing data collected over a one-month time period in one London borough in England in 2016. AWTTC queried whether this proportion is representative of the paediatric population in Wales in 2020. In response, the company provided an additional alternative approach for validation purposes, using data from Wales and prevalence data from the National Autistic Society. This resulted in a prevalence estimate of 3,033 patients in a single year analysis. In comparison the base case budget impact analysis estimates a prevalence of 2,646 patients in Year 1.

- Whilst the approach taken in identifying and proportioning the medicines included in the IR melatonin bundle is transparent and follows a logical approach, it relies on data from England which were collected before the licensing of an IR melatonin oral solution. It is uncertain how prescribing practices differ between England and Wales, and how practices may have changed over time. Given that the unit costs of the preparations available vary considerably between products, there is a potential that such assumptions introduce the potential for bias in IR melatonin cost estimates. For example, if the unit cost of the IR melatonin bundle is adjusted to 79p to reflect Welsh prescribing data for liquid preparations only (i.e. excluding IR melatonin tablets and capsules), which is in line with AWTTC-sought clinical expert opinion, this results in a budget impact of [commercial in confidence figures removed] in Years 1 and 5, respectively.
- If the market share for Circadin® is increased to 80% (AWTTC-sought clinical expert opinion suggests up to 98% of this patient group receive Circadin®), this results in a budget impact of [commercial in confidence figures removed] in Years 1 and 5.
- In keeping with the CUA, the budget impact model adopts pivotal study dosing and assumes dosing for Circadin®. If not reflective of Welsh prescribing practice, this potentially biases estimates. However, upon request, the company provided extensive analyses to explore the influence of alternative dosing assumptions.
- The budget impact considerations are limited to acquisition costs only; other resource use is not included (e.g. monitoring costs and costs associated with adverse events).
- Discontinuation is informed by the same pivotal studies as the CUA model. However, the approach taken is inconsistent.
- The patient number estimates are based on the ASD population only; the SMS population has not been specifically identified; however, the size of this patient group in Wales is likely to be small.

GLOSSARY

Composite Sleep Disturbance Index (CSDI)
A validated tool scoring the frequency and duration of sleep problems reported by parents[16].

Epworth Sleepiness Scale (ESS)
A self-administered questionnaire with eight questions. Caregivers are asked to rate, on a four-point scale (0–3), their usual chances of dozing off or falling asleep while being engaged in eight different activities[20]. The higher the ESS score, the higher that person's average sleep propensity in daily life, or their "daytime sleepiness"[20].

Pittsburgh Sleep Quality Index (PSQI)
The PSQI comprises nine main questions relating to the patient's usual sleep habits during the previous two weeks[20]. It addresses possible reasons for trouble in sleeping as well as daytime behaviour. The caregiver is asked to give the most accurate reply for the majority of his/her own days and nights during this period. An algorithm is used to calculate seven component scores and these are added to give a global PSQI score[20].

Strength and Difficulties Questionnaire (SDQ)
A validated behavioural screening tool comprising 25 items on five psychological attributes, including hyperactivity/inattention, conduct problems, peer relationship problems, emotional symptoms, prosocial behaviour, along with an impact supplement[20]. Validation studies of the SDQ showed three independent domains pertaining to externalising behaviour (sum of hyperactivity/inattention and conduct problems), internalising behaviour (sum of peer relationship problems and emotional symptoms) and prosocial behaviour. The sum of the externalising and internalising attributes (hyperactivity, conduct, peer relationship and emotion subscales) are aggregated to form a Total Difficulties Score (total SDQ); a higher score indicates poorer behavioural adjustment. The third factor, prosocial behaviour is excluded from the total SDQ. A change of any 1 unit across the SDQ range is considered clinically relevant[20].

WHO-5 Wellbeing index
A 25-point wellbeing index that covers positive mood, vitality and general interests. Effect size of 0.4 and over is considered clinically relevant[20].

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