

5.11 MELATONIN (PROLONGED RELEASE), 1 mg and 5 mg tablets, Slenyto[®], Aspen Pharmacare Australia Pty Ltd.

1 Purpose of submission

- 1.1 The submission requested an Authority Required (Telephone) listing for prolonged release melatonin (Slenyto) for the treatment of insomnia in children aged 2-18 years with Autism Spectrum Disorders (ASD) and/or Smith-Magenis Syndrome (SMS).
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis (cost per additional responder; cost per responder year).

Table 1: Key components of the clinical issue addressed in the submission (as stated in the submission)

Component	Description
Population	Children aged 2 to 18 years of age diagnosed with ASD and/or SMS with insomnia
Intervention	Prolonged release melatonin
Comparator	Placebo
Outcomes	Increase in total sleep time; reduction in sleep latency; responder in terms of total sleep time and/or sleep latency
Clinical claim	In patients aged 2-18 years old with ASD and/or SMS, prolonged release melatonin is superior in terms of efficacy compared with placebo for the treatment of insomnia. The submission did not make a claim regarding comparative safety.

Source: Table 1.1, p.12 of the submission

Abbreviations: ASD, Autism Spectrum Disorders; SMS, Smith-Magenis Syndrome

2 Background

Registration status

- 2.1 Prolonged release melatonin was approved by the TGA on 22 May 2020 for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and/or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.

3 Requested listing

- 3.1 The requested listing is presented below. Suggested additions proposed by the Secretariat are in italics and suggested deletions are crossed out with strikethrough.

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Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
PROLONGED RELEASE MELATONIN 1 mg tablet, 60 5 mg tablet, 30	1 1	60 30	5 5	\$ [REDACTED] \$ [REDACTED]	Slenyto® Aspen Pharmacare Australia Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method: <input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Authority Required - Streamlined
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Condition: Insomnia
Indication: Insomnia For the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.
Treatment Phase: Initial
Clinical criteria: Patient must have autism spectrum disorder; OR Patient must have Smith-Magenis Syndrome
AND
Clinical criteria: Patient must have failed to achieve an adequate response to sleep hygiene measures Patient has failed to get sufficient response to sleep hygiene measures
Treatment criteria: The treatment Must be treated in consultation with initiated by a paediatrician, sleep physician, neurologist, or psychiatrist
AND
Population criteria: Patient must be aged between the ages of 2 to 18 years inclusive

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method: <input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Authority Required - Streamlined
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice:

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Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Condition: Insomnia
Indication: Insomnia For the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.
Treatment Phase: Continuing
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition.
Patient must have autism spectrum disorder, OR Patient must have Smith-Magenis Syndrome AND Patient has failed to get sufficient response to sleep hygiene measures
AND
Treatment criteria: The treatment must be treated initiated by a paediatrician, sleep physician, neurologist, or psychiatrist
AND
Treatment criteria: Patient must be aged Treatment must have commenced between the ages of 2 to 18 years inclusive

- 3.2 Although the submission included initial and continuing restrictions, the continuing restriction criteria did not include a response assessment criteria. The product information stated that “after at least 3 months of treatment, the treatment effect should be evaluated, with stopping treatment considered if no clinically relevant treatment effect is seen”. The economic analysis is based on cost per responder, and the financial model included in the submission was based on the premise that only responders would continue with treatment.
- 3.3 The initial restriction criteria limits prescribing to a paediatrician, sleep physician, neurologist, or a psychiatrist. However, insomnia is likely to be managed in general practice. The Pre-Sub-Committee Response (PSCR) argued insomnia in ASD does not resolve with age and the combination of ASD and insomnia as co-morbid conditions and associated safety concerns justified the restriction of initiating melatonin to these practitioners. The ESC considered there was limited justification to limit prescribing of melatonin to specialised practitioners.
- 3.4 The restriction specified an age range of eligibility for treatment with prolonged release melatonin. The evaluation considered it may not be equitable or practical to limit the age for treatment to 18 years, if patients who are achieving a clinical benefit are required to discontinue at this age.
- 3.5 The proposed restriction is for insomnia. It is unclear whether the definition of impaired sleep used in the inclusion criteria in the NEU_CH_7911 trial (see paragraph 6.10) is consistent with the definition of insomnia in children used in clinical practice, and therefore whether the study results will be applicable to the PBS population.

- 3.6 The requested restriction only allows the use of prolonged release melatonin when sleep hygiene measures were insufficient. Adequate information on whether the population included in study NEU_CH_7911 met this criterion was not available. The evaluation considered it is unclear what constitutes 'insufficient' response to sleep hygiene measures for the purposes of the restriction.
- 3.7 The PSCR indicated a willingness on the part of the sponsor to work with the PBAC to devise clinically appropriate restrictions for Slenyto[®] if recommended for listing. The ESC considered it would be appropriate for any potential listing for melatonin to include response criteria for continuing therapy that were based on best clinical practice.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 ASD includes a range of developmental disorders characterised by impairment in functions related to central nervous system maturation, including a varied mixture of impaired capacity for reciprocal socio-communicative interaction and a restricted, stereotyped repetitive repertoire of interests and activities (World Health Organization, 2013). In comparison to typically developing children where prevalence of insomnia is between 1-6%, children with ASD have much higher prevalence, which some authors estimate to be between 40-80% (Cortesi, Giannotti, Ivanenko, & Johnson, 2010).
- 4.2 SMS is a developmental disorder caused by the loss of retinoic acid induced 1 (RAI1) in the chromosome 17 (17p11.2). Common symptoms include mild to moderate intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, and behavioural problems (Elsa & Girirajan, 2008). Many patients with SMS also have ASD comorbidity (Laje et al., 2010).
- 4.3 Melatonin is a hormone secreted by the pineal gland. Melatonin secretion increases soon after the onset of darkness, peaks between 2 a.m. and 4 a.m., and diminishes during the second half of the night. Melatonin is involved in several physiological processes in animals and humans, including modulating synchronisation of the biological clock and promoting sleep. Lower melatonin concentrations have been found in blood and urine samples from children with autism which might explain the abnormal development of sleep/wake cycles (Phillips and Appleton, 2004). Studies show that in people with SMS, melatonin is secreted during the day instead of in the evening or crepuscular hours. This tends to cause an inversion of the circadian rhythm (De Leersnyder et al, 2003; De Leersnyder et al, 2011).
- 4.4 In a developing child, sleep serves multiple functions, including energy conservation, brain growth, memory consolidation, and cognition (Wiggs & Stores, 2001). The consequences of disrupted sleep in children with ASD and/or SMS includes repercussions on the mental and physical health of the children and their carers. Evidence suggests that sleep disorders in children are associated with decreased

educational performance, increased psychopathology and increased risk of self-harm and suicidal ideation (Hysing et al., 2015; Kronholm et al., 2015; Wong et al., 2011). There is a strong correlation in children between insomnia and increased risk of negative health related quality of life (HRQOL) and mental health problems (Combs et al., 2016).

- 4.5 Broadly, for children and adolescents with ASD and/or SMS and sleep disturbance, clinicians should assess for medications and coexisting conditions that could contribute to the sleep disturbance and should address identified issues. All guidelines generally suggest that behavioural strategies and sleep hygiene training should be the first-line treatment approach for sleep disturbance. Clinicians should then offer melatonin if behavioural strategies have not been helpful and contributing coexisting conditions and use of concomitant medications have been addressed, starting with a low dose. At present, most guidelines for the management of insomnia in children with ASD or other neurogenetic disorders (eTG, UpToDate) suggest only short term treatment with melatonin. This is in contrast with the submission, which suggests that, in patients with response, treatment with melatonin could continue indefinitely. The PSCR argued that most guidelines for the target population predate the development of Slenyto[®] and noted that recent guidelines updates from the American Academy of Neurology and Practice guideline state that melatonin should be offered to children and adolescents with ASD if behavioural strategies have not been helpful and further argued a high purity pharmaceutical grade of melatonin should be used when available¹.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated standard supportive care, consisting of behavioural therapy including sleep hygiene, environmental, dietary, and psychological measures, and represented by placebo in the included trial, as the main comparator. The submission stated that this was the appropriate comparator as there are currently no regimens registered or PBS-listed in Australia with demonstrated efficacy, safety and cost-effectiveness in patients with ASD and/or SMS with insomnia.
- 5.2 At present, melatonin may be prescribed primarily via private scripts for the proposed PBS population in Australia, although the extent to which this occurs is unknown. The evaluation noted existing forms of melatonin available via private script may be a secondary comparator.

¹ Buckley, A.W., Hirtz, D., Oskoui, M., Armstrong, M. J *et al* (2020). Practice guideline: Treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology Neurology Mar 2020, 94 (9) 392-404; DOI: 10.1212/WNL.00000000000009033

- 5.3 The PSCR and Pre-PBAC Response argued that alternative forms of melatonin, including Circadin® and extemporaneously compounded preparations were not relevant comparators, as Slenyto® was a specially formulated preparation for paediatric populations and further argued that Circadin® is not indicated for the paediatric population and that compounded preparations are immediate release and are therefore not relevant comparators.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this submission. The clinicians highlighted the importance of an affordable controlled-release formulation of melatonin that is formulated to be easily taken by children with insomnia and highlighted there are few pharmaceutical options for children with this condition. The clinicians stated oral aversion is common in patients with ASD and SMS and it is important for any medication for this population to be tasteless and small in size. The clinicians commented that children with ASD respond differently to melatonin and many require high doses. The clinicians highlighted the significant impact insomnia has on parents and carers quality of life. The clinicians noted children with SMS are often the worst sleepers among their patients and highlighted the very high clinical need for effective treatment options for insomnia in this population.

Consumer comments

- 6.2 No consumer comments were received. However, the PBAC noted input from the Consumer Evidence and Engagement Unit of the Department of Health on this item. This input consisted of a meeting summary with representatives from Smith-Magenis Syndrome Australia. The PBAC noted that SMS Australia estimated the prevalence of SMS was likely to be around 1,000 individuals (based on a prevalence of 1 in 15,000 to 25,000). The PBAC noted almost all individuals with SMS have chronic sleep problems; with night-time waking being the most concerning for parents. This concern is due to both the impact of lack of sleep on mood and learning during the day, as well as the difficulty associated with supervising individuals who may wake and wander during the night. The PBAC noted the advice from SMS Australia that melatonin helps to reduce night-time waking and prolongs sleep but many families remained worried about the lack of regulation around melatonin. The PBAC noted the advice that prolonged release melatonin was the most beneficial formulation for people with SMS as it was primarily night-time waking that is the issue, rather than sleep latency. The PBAC noted a high proportion of patients with SMS are currently using various formulations of melatonin.

Clinical trial

6.3 The submission was based on one head-to-head trial comparing prolonged release melatonin to placebo (n=125; NEU_CH_7911), in children with ASD and/or neurodevelopmental disabilities caused by neurogenetic diseases (including SMS, Angelman syndrome, Bourneville’s disease [tuberous sclerosis]) aged between 2 and 18 years with impaired sleep. Only 4 of the enrolled participants had SMS and no other participants with neurogenetic diseases were recruited.

6.4 Details of the trial presented in the submission are provided in the table below.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
NEU_CH_7911	A randomized, placebo-controlled study to investigate the efficacy and safety of Circadin to alleviate sleep disturbances in children with neurodevelopmental disabilities	19 June 2018
	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 Psychopharmacol. 2018 Dec;28(10):699-710
	Malow BA, Findling RL, Schroder CM, et al. Sleep, Growth, and Puberty After 2 Years of Prolonged-Release Melatonin in Children With Autism Spectrum Disorder.	J Am Acad Child Adolesc Psychiatry. 2020 Jan 23:S0890-8567(20)30034-4.
	Schroder CM, Malow BA, Maras A, et al. Pediatric Prolonged-Release Melatonin for Sleep in Children with Autism Spectrum Disorder: Impact on Child Behavior and Caregiver's Quality of Life.	J Autism Dev Disord. 2019 Aug;49(8):3218-3230.
	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 Nov;56(11):948-957.e4.

Source: Table 2.3, pp.52-53 of the submission

6.5 The key features of the NEU_CH_7911 trial are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
NEU_CH_7911	125	Randomised, double blinded, multi centre, 13 week double blind period followed by up to 2 years open label treatment	High	Children aged between 2-18 years with ASD and/or SMS, with impaired sleep	Total sleep time; Sleep latency; Responder (increase in total sleep time ≥45 min and/or reduction in sleep latency ≥15 min)	Total sleep time and/or sleep latency responders

Source: Table 2.4, p.56 of the submission; NEU_CH_7911 CSR

Abbreviations: ASD, Autism Spectrum Disorders; SMS, Smith-Magenis Syndrome

6.6 The NEU_CH_7911 study had a potentially high risk of attrition bias due to incomplete outcome data. There were differences between treatment arms in the numbers of parents completing valid sleep and nap diaries, with lower completion rates in the placebo arm (79% vs 90% in the melatonin treatment arm). Information from the sleep and nap diaries informed both the primary (total sleep time) and secondary (sleep latency) outcomes upon which the submission was based.

- 6.7 The NEU_CH_7911 randomised trial included an initial 4 week sleep hygiene period with no pharmacological treatment. In this phase, children who did not have a documented history of sleep hygiene and behavioural intervention at screening underwent 4 weeks of basic sleep hygiene and behavioural intervention. This period also served as a wash-out period from any hypnotics; a gradual withdrawal took place during the first 2 weeks and a complete withdrawal of prohibited medications took place during the last 2 weeks. Patients who did not respond to sleep hygiene measures, or who had a documented history of non-response, were eligible to continue into the double-blind treatment period. The placebo arm of the trial may not adequately represent standard supportive care, which was the nominated comparator. No behavioural measures were allowed to continue during the trial period, however in practice sleep hygiene training or psychotherapeutic measures such as behavioural therapies are likely to continue to be offered. The trial was therefore unable to derive the added benefit of melatonin versus standard supportive care.
- 6.8 The double blind period commenced with a 2 week single-blind placebo run-in, followed by a randomised double-blind efficacy and safety study of 13 weeks prolonged release melatonin (2 mg with optional escalation to 5 mg after 3 weeks) or placebo treatment (with optional dose escalation as in the active arm). Children then continued on 2 mg or 5 mg of prolonged release melatonin or placebo for the remaining 10 weeks of double-blind treatment, with an efficacy assessment visit at week 15 (i.e. following 13 weeks of double blind treatment).
- 6.9 All completers then received open label prolonged release melatonin, according to the final dose in the double-blind phase, for 91 weeks with optional dose adjustment (2, 5 or 10 mg/day) after the first 13 weeks of open label treatment. A 2-week single-blind placebo period (withdrawal phase) then followed. There is a lack of comparative evidence supporting the use of a 10 mg dose of prolonged release melatonin.
- 6.10 The trial enrolled children 2 to 17.5 years with a confirmed history of either ASD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5/4) criteria or International Classification of Diseases 10th Revision (ICD-10), or neurodevelopmental disabilities caused by neurogenetic diseases (including SMS); and sleep problems including: a minimum of 3 months of impaired sleep defined as ≤ 6 hours of continuous sleep and/or ≥ 0.5 hour sleep latency from light off in 3 out of 5 nights per week for 2 weeks based on parent reports and patient medical history. It is unclear whether the definition of impaired sleep used in the trial inclusion criteria is consistent with the definition of insomnia in children used in clinical practice. It is also unclear whether the trial population had experienced an inadequate response to sleep hygiene measures, as required under the requested restriction.
- 6.11 The clinical relevance of a responder as defined in the submission (increase in total sleep time ≥ 45 min and/or reduction in sleep latency ≥ 15 min per night after 13 weeks of double-blind treatment) was unclear. The total change in sleep time and/or sleep latency was assessed as an absolute change from baseline (rather than a relative

change from baseline), and the clinical relevance of an absolute change is likely to vary based on the age of the child. There is large variability in normal sleep durations for normally developing children within the age range requested, and the absolute treatment difference specified in the responder analysis is less than the natural variation in sleep times in children across the included age groups. It is difficult to interpret how beneficial a small change in total sleep time or sleep latency is.

Comparative effectiveness

6.12 Results for change from baseline in total sleep time after 13 weeks of double blind treatment, the primary outcome in the NEU_CH_7911 trial, are summarised in Table 4.

Table 4: Change from baseline in total sleep time (FAS)

	n	Prolonged release melatonin (N=58)	n	Placebo (N=61)	Treatment difference (95% CI)
Baseline	-	NR	-	NR	-
Total sleep time week 13, mean minutes per night (SD)		507.57 (86.77)		487.89 (92.10)	-
Change from baseline, adjusted treatment means (SE)	52	51.03 (10.46)	48	18.71 (10.82)	32.32 (2.38, 62.26)

Source: Table 8, p.67 NEU_CH_7911 CSR; Table 14.2.1.3, pp.102-103, Section 141 and 142 tables 2 year data update.pdf

Abbreviations: FAS, full analysis set; SD, standard deviation; SE, standard error

Note: Analysis conducted on the full analysis set using a mixed-effects model for repeated measures (MMRM) model with the value at week 3 and week 13 as the dependent variable, with fixed effects for visit, the mean baseline value, randomised treatment and the mean baseline value and randomised treatment both nested within visit

6.13 Total sleep time was calculated based on the mean total daily sleep time recorded in the sleep and nap diaries over the 14 days prior to the assessment point. After 13 weeks of double blind treatment, children in the prolonged release melatonin treatment group achieved a mean change of 51 minutes of increase in total sleep time per night, compared to 19 minutes for children in the placebo group. The treatment difference was 32 minutes, which was statistically significant. The estimate was associated with wide confidence intervals, with the lower bound being only 2.4 minutes.

6.14 A number of secondary and exploratory outcomes were assessed, including additional sleep and nap diary variables and patient reported outcome measures. Of the secondary outcomes, only sleep latency and the externalising behaviour subscore of the Strengths and Difficulties Questionnaire (SDQ) showed statistically significant improvements associated with treatment with melatonin. There was no statistically significant difference between treatment groups for other variables including duration of wake time, number of awakenings, longest sleep period, total time in bed per night, sleep disturbance (Composite Sleep Disturbance [CSDI] score), social functioning (Children’s Global Assessment [CGAS] score), or other scores on the SDQ.

6.15 Results of secondary outcomes are presented in the table below.

Table 5: Change from baseline in the secondary outcomes in the NEU_CH_7911 trial (FAS)

	n	Prolonged release melatonin (N=58)	n	Placebo (N=61)	Treatment difference (95% CI)
Sleep latency (minutes)	52	-37.77 (6.82)	48	-12.57 (7.01)	-25.20 (-44.61, -5.80)
Duration of wake time (minutes)	47	-10.32 (2.41)	42	-10.26 (2.5)	-0.06 (-6.98, 6.86)
Number of awakenings	52	-0.31 (0.09)	48	-0.20 (0.09)	-0.11 (-0.36, 0.14)
Longest sleep period (minutes)	51	71.99 (14.76)	44	30.01 (15.49)	41.98 (-0.57, 84.53)
Total time in bed per night (minutes)	52	13.30 (8.98)	48	8.58 (9.23)	4.72 (-20.82, 30.26)
Sleep disturbance (CSDI score)	55	-2.44 (0.35)	49	-1.52 (0.37)	-0.92 (-1.93, 0.09)
Social functioning (CGAS score)	55	1.96 (1.33)	49	1.84 (1.36)	0.13 (-3.64, 3.89)
Behaviour (SDQ total score)	54	-0.84 (0.39)	49	0.17 (0.41)	-1.01 (-2.12, 0.11)
Externalising behaviour (SDQ subscore)	54	-0.70 (0.24)	49	0.13 (0.26)	-0.83 (-1.54, -0.13)
Impact score (SDQ subscore)	54	-0.57 (0.28)	49	0.16 (0.30)	-0.74 (-1.55, 0.08)

Source: Section 2.5.1, pp.75-84 of the submission; Table 8, p.67 NEU_CH_7911 CSR; Table 14.2.1.3, pp.102-103, Section 141 and 142 tables 2 year data update.pdf

Abbreviations: CI, confidence interval; CGAS, Children's Global Assessment Scale; CSDI, Composite Sleep Disturbance Index; FAS, full analysis set; SD, standard deviation; SDQ, Strengths and Difficulties Questionnaire; SE, standard error

Note: Analysis conducted on the full analysis set using a mixed-effects model for repeated measures (MMRM) model with the value at week 3 and week 13 as the dependent variable, with fixed effects for visit, the mean baseline value, randomised treatment and the mean baseline value and randomized treatment both nested within visit

6.16 Results for the exploratory responder analyses, the outcomes used in the economic analyses, are summarised in Table 6.

Table 6: Proportion of responders (TST and sleep latency) (FAS)

	Prolonged release melatonin (n=58) N (%)	Placebo (n=61) N (%)	Odds ratio (95% CI)	Risk difference (95% CI)
Total sleep time responders (≥45 min increase in total sleep time per night from baseline)				
Week 3	19 (32.8)	11 (18.0)	2.6 (0.99, 6.58)	-0.15 (-0.30, 0.01)
Week 13 (end double blind period)	22 (37.9)	10 (16.4)	5.8 (1.80, 18.36)	-0.22 (-0.36, -0.06)
Sleep latency responders (≥15 min decrease in sleep latency per night from baseline)				
Week 3	29 (50.0)	15 (24.6)	4.3 (1.7, 10.5)	-0.25 (-0.41, -0.08)
Week 13 (end double blind period)	37 (63.8)	20 (32.8)	3.8 (1.8, 8.3)	-0.31 (-0.46, -0.13)

Source: Table 2.23, p.87 of the submission

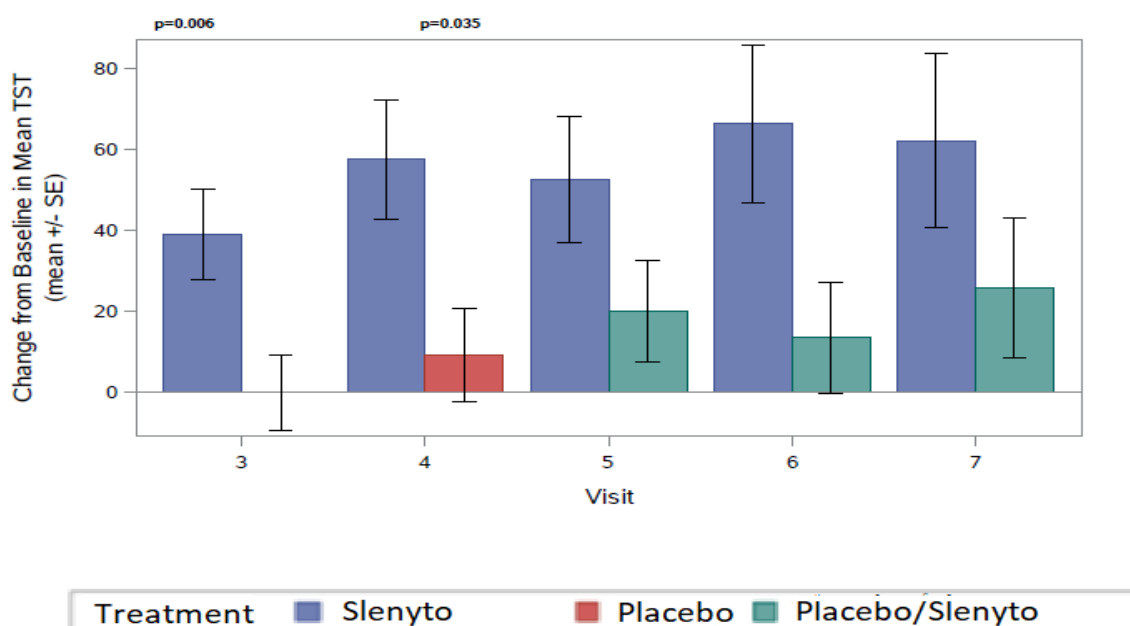
6.17 Response rates for both total sleep time and sleep latency were statistically significantly different between treatment groups in favour of prolonged release melatonin after 13 weeks of treatment.

6.18 The responder rates applied in the economic analysis were based on the percentage of participants who were either a total sleep time and/or sleep latency responder. The data for this was not presented in the Clinical Study Report, but was reported (percentages only) in one of the publications arising from the key trial (Gringras et al., 2017). At the end of the double blind treatment period, these percentages were

reported as 68.9% versus 39.3% in the prolonged release melatonin and placebo treatment arms respectively.

- 6.19 Response rates based on the 52 week assessment in the open label phase were used in the economic analysis, both for the cost per responder at 1 year analysis and to inform the extrapolation in the cost per responder-year analysis. These results were not provided in the submission, however the value applied in the economic model for the proportion of responders at 52 weeks, in the treatment group who had originally been randomised to melatonin, was 72.4%.
- 6.20 The submission stated that the change from baseline for reduction in sleep latency was maintained for the duration of the open label period. The ESC noted the original placebo group did not achieve the same improvements in total sleep time (Figure 1) or sleep latency (Figure 2) as the original melatonin group during the open label period. It is unclear why this pattern of results occurred; some of the treatment effect during the double-blind period may have been due to on-trial behaviour and/or how missing data was adjusted for in the analysis.

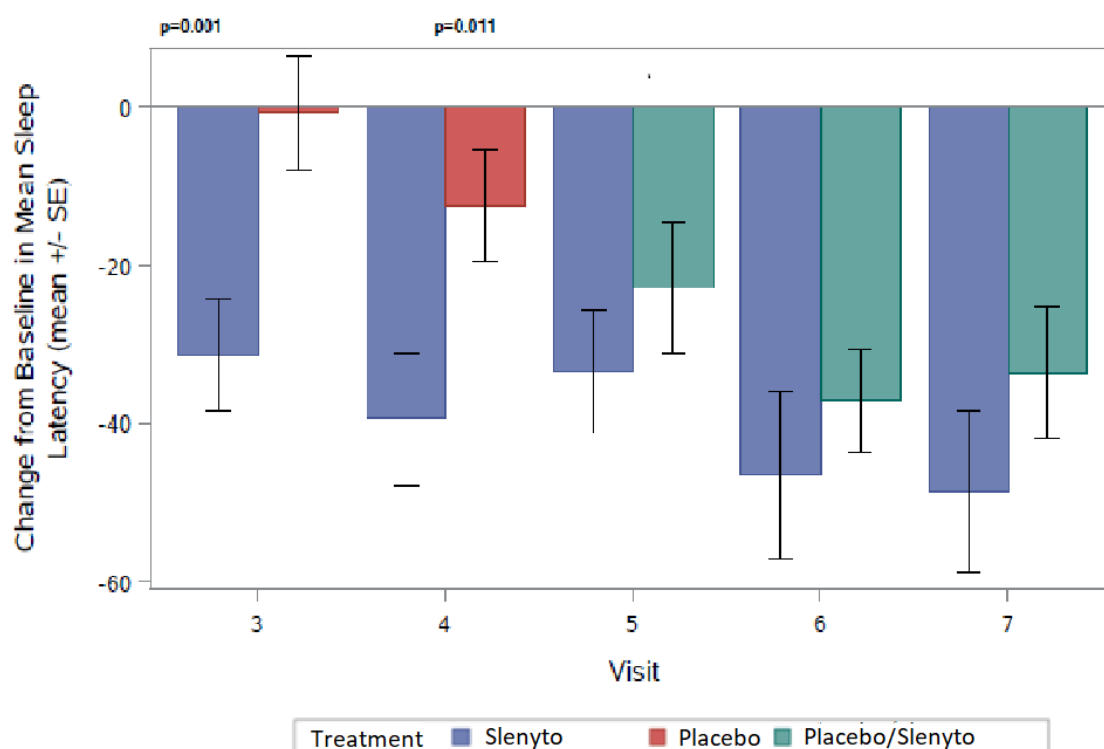
Figure 1: Change from baseline in mean total sleep time (minutes) per night during the double-blind and open-label periods



Source: Figure 2.6, p.94 of the submission

Notes: Visit 3: 3 weeks (double-blind), Visit 4: 13 weeks (double-blind); Visit 5: 26 weeks (open label); Visit 6: 39 weeks (open label); Visit 7: 52 weeks (open label)

Figure 2: Change from baseline in mean sleep latency (minutes) during the double-blind and open-label periods



Source: Figure 2.7, p.95 of the submission

Notes: Visit 3: 3 weeks (double-blind), Visit 4: 13 weeks (double-blind); Visit 5: 26 weeks (open label); Visit 6: 39 weeks (open label); Visit 7: 52 weeks (open label)

6.21 The ESC noted the arguments in the submission and PSCR, however agreed with the commentary and remained uncertain whether the definition of responder, as defined in the submission, was clinically relevant. The ESC was concerned that the wide confidence margins on the primary outcome, the unreasonable assumption that a single definition of responder was meaningfully applicable to the entire age range, and lack of statistically significant changes to the majority of secondary behavioural variables associated with the observed changes in total sleep time and sleep latency, all created substantial uncertainty as to the clinical relevance of the results and responder definition.

Comparative harms

6.22 A summary of adverse events reported during the double blind phase of trial NEU-CH-7911 is reported in Table 7 below.

Table 7: Summary of adverse events in the NEU_CH_7911 trial (safety set)

	Double blind phase	
	Prolonged release melatonin N=60	Placebo N=65
Number of patients with at least one treatment emergent adverse event	51 (85%)	50 (76.9%)
Number of patients with at least one treatment related adverse event	12 (20%)	11 (16.9%)
Number of patients with at least one severe adverse event	15 (25%)	13 (20%)
Commonly reported adverse events		
Somnolence	17 (28.3%)	8 (12.3%)
Fatigue	15 (25.0%)	12 (18.5%)
Mood swings	10 (16.7%)	11 (16.9%)
Upper respiratory tract infection	9 (15.0%)	7 (10.8%)
Vomiting	8 (13.3%)	10 (15.4%)
Agitation	11 (18.3%)	7 (10.8%)
Headache	8 (13.3%)	4 (6.2%)
Cough	7 (11.7%)	5 (7.7%)
Dyspnoea	6 (10.0%)	4 (6.2%)
Rash	3 (5.0%)	3 (4.6%)
Commonly reported severe adverse events		
Somnolence	6 (10.0%)	3 (4.6%)
Fatigue	4 (6.7%)	2 (3.1%)
Mood swings	4 (6.7%)	5 (7.7%)
Most commonly reported treatment related adverse events		
Somnolence	7 (11.7%)	2 (3.1%)
Fatigue	2 (3.3%)	3 (4.6%)
Mood swings	1 (1.7%)	4 (6.2%)

Source: Table 2.24, pp.89-90; Table 2.25, p.90; Table 2.26, p.91 of the submission

- 6.23 During the double-blind phase, severe adverse events were reported by 15 (25.0%) patients in the prolonged release melatonin group and 13 (20.0%) patients in the placebo group. Severe adverse events including somnolence and fatigue were more commonly reported in the prolonged release melatonin group.
- 6.24 Treatment-related adverse events were reported by 12 (20%) patients (28 events) in the prolonged release melatonin group and 11 (16.9%) patients (17 events) in the placebo group. Somnolence and fatigue were more commonly reported as treatment related adverse events in the prolonged release melatonin group compared to placebo, whereas mood swings were more commonly reported as treatment-related adverse event in the placebo group.
- 6.25 The submission assessed growth as a potential adverse event of special interest. No statistically significant differences between patients treated with prolonged release melatonin and placebo were noted, however a period of 13-26 weeks is too brief to reliably assess growth outcomes. The impact of long-term use of melatonin on growth remains unclear.
- 6.26 The submission presented the results of the Tanner assessments of pubertal development. There was no apparent differences in pubertal development between patients treated with prolonged release melatonin and placebo; however, due to the

relatively short double blind period with crossover into active treatment for the open label period, it is difficult to ascertain the possible effects of prolonged release melatonin on pubertal development. Longer term safety studies are required to determine whether the long-term use of melatonin may have adverse effects on pubertal development. The PSCR and the ESC acknowledged the need for longer term safety data.

Benefits/harms

6.27 On the basis of the direct evidence presented in the submission (13 weeks of double blind treatment in NEU_CH_7911), for every 100 children (aged 2 to 18 years) with ASD and/or SMS and insomnia treated with prolonged release melatonin in comparison with placebo:

- Patients would experience, on average, approximately 32 minutes additional sleep time per night.
- Approximately 22 more patients would achieve an increase of ≥ 45 minutes of total sleep time per night.
- Approximately 31 more patients would achieve a reduction of ≥ 15 minutes in sleep latency.
- Approximately 16 more patients would experience somnolence during the day (sleepiness or drowsiness).
- Approximately 7 more patients would experience fatigue.

Clinical claim

6.28 The submission described prolonged release melatonin (2, 5, or 10 mg) as superior in terms of efficacy compared with placebo. No claim was made as to comparative safety.

6.29 Whilst a statistically significant treatment difference was observed in favour of prolonged release melatonin in terms of total sleep time, the clinical relevance of the treatment difference was unclear (32 minutes per night). Only 48/61 (79%) patients in the placebo arm, and 52/58 (90%) patients in the melatonin arm, were included in the calculation of the primary outcome. The estimate was associated with wide confidence intervals, with the lower bound being only 2.4 minutes per night. Further, these changes in sleep time were not accompanied by significant changes in patient or carer daytime functioning, considered to be important components of any treatment for insomnia. The PSCR noted that according to the WHO Five Well-Being Index (WHO-5) 13 weeks of Slenyto[®] treatment significantly improved caregivers' quality of life compared with placebo ($p=0.01$). The ESC noted the WHO-5 was an exploratory outcome and also questioned the clinical significance of the observed improvement in carer quality of life (2.17 points on a 25 point scale). The Pre-PBAC Response argued the observed statistically significant improvements in externalising behaviour and caregivers' quality of life (on the WHO-5 scale) support the clinical

relevance of the observed statistically significant differences in sleep-based endpoints.

- 6.30 The responder analysis, which forms the basis of the economic and financial analyses, was an exploratory outcome in the NEU_CH_7911 trial. The clinical relevance of a responder as defined in the submission was unclear. The total change in sleep time and/or sleep latency was not assessed relative to baseline, and the clinical relevance of an absolute change is likely to vary based on the age of the child. The ESC noted there is huge variability in normal sleep durations for normally developing children within the age range requested (2-18 years), and the absolute treatment difference specified in the responder analysis is less than the natural variation in sleep times in children across the included age groups. The PSCR argued that the responder criteria were valid based on use in studies of tasimelton and zopiclone. However, the ESC noted that the tasimelton and zopiclone studies were both in adults, and so the relevance in a 2-18 year old age group remains unclear. The ESC therefore agreed with the evaluation that proportional (i.e., relative) change based on baseline sleep may have been more appropriate.
- 6.31 The PSCR argued the observed adjusted mean improvement of 32.4 minutes of TST was clinically relevant and claimed children with ASD tend to sleep 32.8 minutes less per night than their typically developed peers, based on a reference to a clinical trial of melatonin (clinicaltrials.gov identifier NCT01906866). However the ESC noted the provided reference did not appear to contain this statement and could not verify this claim.
- 6.32 The recommended starting dose is 2 mg. If an inadequate response has been observed, the dose should be increased to 5 mg, with a maximal dose of 10 mg. Although this is consistent with the product information, the 10 mg dose was only permitted during the open label phase of the included clinical trial, and so there is a lack of comparative and longer term data to support the treatment benefit of this dose.
- 6.33 The diagnosis of insomnia may be difficult in children. It is unclear how insomnia is diagnosed in children and adolescents in Australian clinical practice. The submission suggested that the diagnosis should be based on the DSM-V criteria for insomnia. The trial did not use standardised diagnostic criteria for insomnia as an inclusion criteria, but instead used a definition for 'impaired sleep'.
- 6.34 Treatment with prolonged release melatonin was associated with a higher incidence of adverse events including mood swings, somnolence, and fatigue, compared with placebo. Several patients in the trial had dose reductions due to increases in daytime fatigue. Due to the relatively short double blind period with crossover into active treatment for the open label period, it is difficult to ascertain the possible longer term effects of prolonged release melatonin. One potential concern is the effect of long-term treatment with melatonin on pubertal development. Longer term safety studies are required to determine whether the long-term use of melatonin may have adverse

effects on pubertal development. The ESC considered that based on the available evidence and lack of long-term safety data, a claim of inferior comparative safety to placebo was reasonable for prolonged release melatonin.

- 6.35 The PBAC considered that the claim of superior comparative effectiveness was reasonable but the clinical significance of the benefit was uncertain.
- 6.36 The PBAC noted the submission did not include a comparative safety claim but considered that a claim of inferior comparative safety would be reasonable.

Economic analysis

- 6.37 The submission presented a trial-based economic evaluation based on the NEU_CH_7911 randomised trial, and a modelled economic evaluation based on cost per year of response, extrapolated over a 9-year time horizon. The type of economic evaluation presented was a cost-effectiveness analysis, reported as a cost per responder and cost per additional responder year. The pre-PBAC response stated the base case economic analysis in the submission was the cost per responder and cost per responder-year at 2 years.
- 6.38 Table 8 summarises the key components of the economic evaluation.

Table 8: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness analysis
Outcomes	Response (defined as an increase in total sleep time of at least 45 minutes per night, and/or reduction in sleep latency of at least 15 minutes per night)
Time horizon	2 years for the cost per responder analysis and 9 years for the cost per responder year analysis, extrapolated from 13 weeks in the double blind period in the trial
Methods used to generate results	Trial-based analysis, with assumptions used to extrapolate beyond the duration of the trial
Software package	Excel 2010

Source: Table 3.3, p.117 of the submission

- 6.39 A summary of the key drivers of the analysis is presented in Table 9 below.

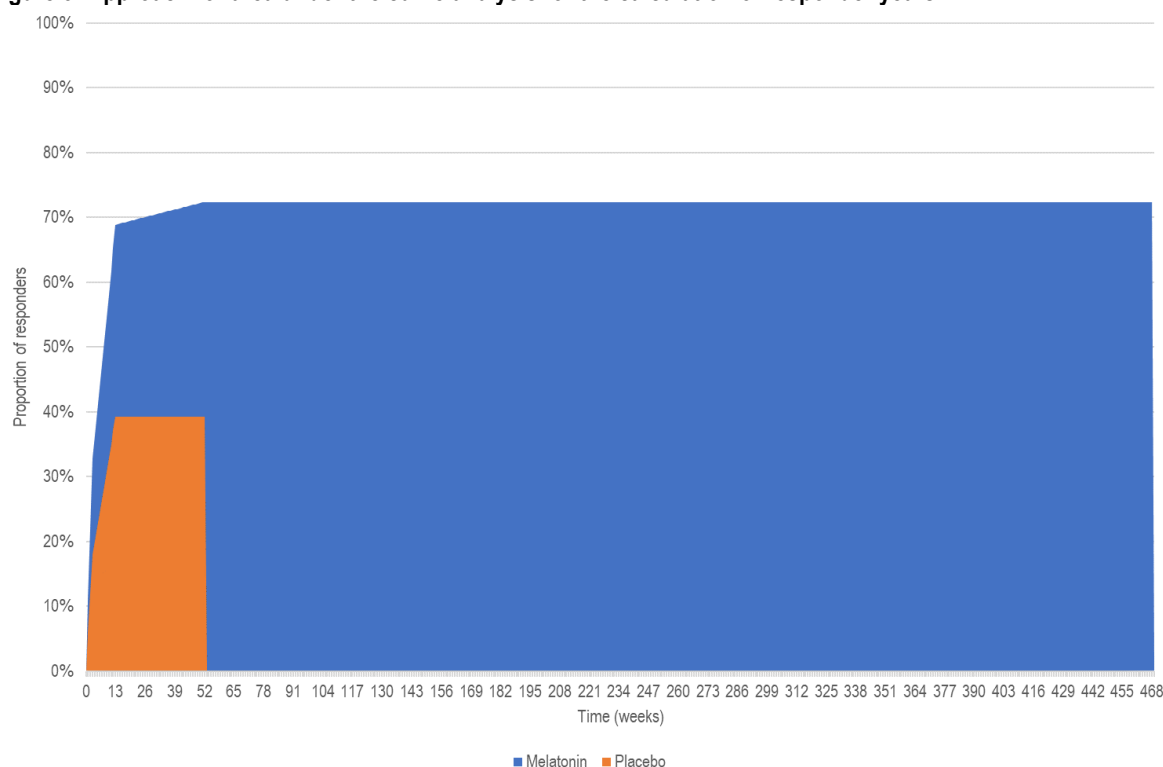
Table 9: Key drivers of the model

Description	Method/Value	Impact
Extrapolation	Treatment effect continued beyond 13 week trial period for up to 9 years. The base case applied response rates observed in the group originally randomised to prolonged release melatonin at the 52-week open label time point, and assumed that these would be maintained for 2 or 9 years, whilst the response rate in the placebo group was assumed to be zero after 52 weeks. The extrapolated responder rate for melatonin is likely to be significantly higher than what will be observed in clinical practice. Further, extrapolating the treatment effect assumes that this effect will be broadly maintained over long periods of time. There was no clinical evidence provided in the submission to support this assumption.	High, favours prolonged release melatonin
Treatment discontinuations	Treatment discontinuations in the economic analysis were informed by a time on treatment curve derived from the proportions of patients in the treatment arm who received melatonin during both the double blind and open label periods of the trial, and who discontinued treatment for any reason. This was used to derive cost of melatonin. The submission applied a logarithmic trendline to the observed data in Excel to extrapolate beyond the trial period. The decision to extrapolate proportion of continuing patients to inform cost of treatment with melatonin was not described nor justified in the submission. This results in extremely favourable assumptions; by the end of the 9-year time horizon, only 48% of patients remain on treatment (and thus accumulate drug costs), but 72.4% of patients continue to achieve a response.	High, favours prolonged release melatonin
Outcomes	In both the trial based analysis estimating cost per responder, and the extrapolated analysis estimating cost per responder-year, the outcome was 'responder'. Given the large range of normal sleep durations for children within the age in the trial, the absolute treatment difference specified in the responder analysis is less than the natural variation in sleep times in children across the included age groups in the trial. It may also not be appropriate to collapse both total sleep time and sleep latency to form a definition of responder, as differences in sleep latency tended to drive improvements in total sleep time. A proportional change based on baseline sleep may have been more appropriate. At present it is difficult to know how beneficial a small change in total sleep time or sleep latency is. The endpoints of cost per responder and cost per responder year, are therefore difficult to interpret.	Unclear
Cost of melatonin	Drug costs were applied based on the average dose in the NEU_CH_7911 trial, and using a split over dose strengths of 29% (1 mg) and 71% (5 mg). The economic analysis was sensitive to the split across doses, and the average dose applied. The dose likely to be used in practice is unclear.	Unclear

Source: Compiled during the evaluation

6.40 In the 9-year responder year analysis, the proportion of melatonin responders at 52 weeks was assumed to be maintained to 9 years; however the placebo response was assumed to be lost after 52 weeks. Figure 3 details the area under the curve analysis used to calculate responder years over a 9 year time horizon.

Figure 3: Approach for area under the curve analysis for the calculation of responder years



Source: Constructed during the evaluation using 'Slenyto PRM Section 3 workbook

6.41 There is significant uncertainty associated with the extrapolation. Although the submission stated that the 52 week treatment effect was attenuated over years 2-9 of the 9-year time horizon (and this was reiterated in the PSCR), this was not actually applied in the analysis. In Figure 1, the proportion of responders at 52 weeks in the treatment group originally randomised to receive prolonged release melatonin is maintained for the duration of the analysis, whilst the placebo response was assumed to be 0 after the end of year 1. The ESC considered this was not reasonable. The ESC noted that discontinuations based on the pivotal trial and open label extension (OLE) found that by the end of that period only 48% of the cohort was on treatment. On that basis, the ESC considered the assumption that the 72% of responders at week 52 will maintain that benefit for 9 years was implausible and not supported by the available data. The Pre-PBAC Response noted there was an increase in responder rate observed between Week 13 and Week 52 of the clinical trial and a trend was observed that responder rate increases over time and argued the attenuation of the responder rate assumption applied in the model (visible in Figure 3) was conservative. The PBAC agreed with the ESC and considered that it was implausible that patients who achieved a response at Week 52 would maintain the response for 9 years and further noted no evidence was presented to support this assumption.

6.42 The economic analysis assumed all patients receive an average daily dose of 5.3 mg. This dose was also used to derive the average daily cost of treatment with prolonged release melatonin. The source of the dose data was unclear in the submission. The

PSCR clarified that at the end of the OLE phase, 29% of study participants were on 2 mg, 46% were on 5 mg and 24% were on the 10 mg dose and the applied 5.3mg dose was the weighted average and further noted that if the proportions from the double-blinded phase were used (58% on 5 mg and 42% on 2 mg) that the average dose would be 3.74 mg. The ESC considered the likely dose distribution of melatonin in clinical practice was highly uncertain.

6.43 The results of the stepped economic analysis, including analyses calculated during the evaluation to address errors, are provided in Table 10 below.

Table 10: Results of the stepped economic evaluation with analyses conducted during the evaluation to address errors in the submission*

Step and component	Prolonged release melatonin	Placebo	Increment
Step 1a: Proportion of total sleep time and/or sleep latency responders at 13 weeks (based on the double blind period of trial NEU_CH_7911); melatonin drug costs only			
Costs	\$█	\$0	\$█
Responders	68.9%	39.3%	29.6%
Incremental cost/additional responder			\$█ ¹
Step 1b: Proportion of total sleep time and/or sleep latency responders at 52 weeks (based on the double blind and open label periods of trial NEU_CH_7911 for placebo and melatonin arms respectively); melatonin drug costs only			
Costs	\$█	\$0	\$█
Responders	72.4%	39.3%	33.1%
Incremental cost/additional responder			\$█ ²
Step 2: Proportion of responders extrapolated to 104 weeks (based on the double blind and open label periods of trial NEU_CH_7911 for placebo and melatonin arms respectively); melatonin drug costs only			
Costs	\$█	\$0	\$█
Responders	72.4%	39.3%	33.1%
Incremental cost/additional responder			\$█ ²
Step 3: Responder years, based on area under the curve analysis of proportion of responders at 52 weeks (based on the double blind and open-label periods of trial NEU_CH_7911); melatonin drug costs only			
Costs	\$█	\$0	\$█
Responder years	0.27	-	0.27
Incremental cost/responder year gained			\$█ ²
Step 4: Responder years extrapolated to 9 years (assuming response at 52 weeks is maintained for melatonin; but lost for placebo); melatonin drug costs only			
Costs (discounted)	\$█	\$0	\$█
Responder years (discounted)	4.96	-	4.96
Incremental cost/responder year gained			\$█ ¹

Source: Slenyto PRM Section 3 Workbook 3.11.2020.xls

* There were two errors in the economic analysis. A discount of 5% was applied once to outcomes accrued over 9 years, rather than applying an annual (compounding) discount. The submission also used 37 weeks rather than 39 weeks to make up the remaining weeks in the first year after the 13-week double blind period. These were corrected during the evaluation.

The redacted values correspond to the following ranges:

¹ \$0 to < \$5,000

² \$5,000 to < \$15,000

6.44 Based on the submission's approach, the incremental cost per additional responder over 2 years is \$5,000 to < \$15,000 and the incremental cost per responder year gained over 9 years is \$0 to < \$5,000.

6.45 The results of key sensitivity analyses are summarised below.

Table 11: Results of sensitivity analyses calculated during the evaluation

Analyses	Incremental cost	Incremental responder years	ICER
Base case (discounted)	\$ [redacted]	4.96	\$ [redacted] ¹
Incremental treatment effect applied years 1-9 (placebo effect doesn't disappear after 12 months)	\$ [redacted]	2.42	\$ [redacted] ²
Treatment effect attenuation (base case 1.84; no attenuation) Lower bound 95% confidence interval: 1.26 Convergence of treatment effect: 1.00	\$ [redacted] \$ [redacted]	4.27 3.96	\$ [redacted] ¹ \$ [redacted] ¹
Dose of melatonin (base case 5.3 mg/day, 29% 1 mg x [redacted] ³ and 71% 5mg x [redacted] ³ scripts). <ul style="list-style-type: none"> • 2 mg/day (100% 1 mg x [redacted]³ scripts) • 5 mg/day (100% 5 mg x [redacted]³ scripts) • 10 mg/day (100% 5 mg x [redacted]³ scripts) 	\$ [redacted] \$ [redacted] \$ [redacted]	4.96 4.96 4.96	\$ [redacted] ¹ \$ [redacted] ¹ \$ [redacted] ¹

Source: Calculated during the evaluation using Slenyto PRM Section 3 workbook.

The redacted values correspond to the following ranges:

¹ \$0 to < \$5,000

² \$5,000 to < \$15,000

³ < 500

6.46 The results of the sensitivity analysis show that the economic analysis was most sensitive to the inclusion of the incremental treatment effect over placebo, and the cost associated with different doses of melatonin.

6.47 The ESC considered the model was not a reasonable basis for assessing the cost-effectiveness of prolonged release melatonin in the requested population. In particular, the ESC considered the cost per responder approach to be problematic as the definition of responder used in the model was of uncertain clinical significance (paragraph 6.21 refers) and further considered the model structure to be overly simplistic and numerous assumptions favoured prolonged release melatonin. Therefore, the ESC considered an alternative basis for the economic model (addressing issues raised in paragraphs 6.39 to 6.42) may be more appropriate. However, the ESC also acknowledged that a QALY based approach would be challenging (but not impossible) due to the need for multiple transformations of the available data to support such an approach. The ESC noted QALYs were modelled for a submission for Slenyto® versus immediate release melatonin to the Scottish Medicines Consortium (SMC, 2020²) and further noted that submission was not recommended for use within NHS Scotland as the company did not present a sufficiently robust economic analysis to gain acceptance by the SMC. The Pre-PBAC Response argued it would be inherently difficult to model the cost-effectiveness of prolonged release melatonin in the requested populations on a cost per QALY basis from the sleep-based endpoints in the clinical trials and further argued deriving robust

² Scottish Medicines Consortium (SMC), 2020. Assessment document – melatonin 1 mg and 5 mg prolonged-release tablets (Slenyto), Flynn Pharma Ltd. Available online at <https://www.scottishmedicines.org.uk/medicines-advice/melatonin-slenyto-resubmission-smc2306/>

utility values to inform a model for this population would be inherently uncertain and would require a number of assumptions to be made.

Drug cost/patient/year

Table 12: Drug cost per patient for proposed and comparator drugs (at proposed DPMQ)

	Prolonged release melatonin Trial dose and duration	Prolonged release melatonin Economic analysis	Prolonged release melatonin Financial estimates
Mean dose	5.3 mg/day	5.3 mg/day	5.3 mg/day
Mean duration	Mean total time on prolonged release melatonin treatment across both double blind and open label phases was 547.4 days (range 14 to 770 days); assume 100% compliance	270.4 weeks over a 9 year (468 week) time horizon cost per responder year analysis, incorporating discontinuations	Assumed total treatment duration of 18 months. 100% initial script 3 months 69% continuing script for additional 15 months
Average cost/patient/week	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Average cost/patient/year	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Compiled during the evaluation using NEU_CH_7911 CSR; Slenyto PRM Section 3 workbook; Slenyto PRM Section 4 workbook

- 6.48 In the NEU_CH_7911 trial, the submission noted that the average dose per day was 5.3 mg (source not provided). The NEU_CH_7911 trial used only 1 mg tablets for all dosing, but the submission calculated the population split over the equivalent 1 mg and 5 mg tablets that will be available if PBS listed, based on the doses used (29% and 71% for 1 mg and 5 mg tablets respectively). The submission used this to calculate a weighted average cost per day, based on the proposed DPMQ (\$ [REDACTED] per day). This gives an average cost of \$ [REDACTED] per week, or \$ [REDACTED] per year.
- 6.49 In the economic analysis, the same average cost of \$ [REDACTED] per day was applied over the 9-year time horizon of the economic analysis (cost per responder year), with discontinuations informed by a time on treatment curve extrapolated from observed treatment rates in the NEU_CH_7911 clinical trial. Taking discontinuations into account, the average weekly cost was \$ [REDACTED] over the life of the analysis, which results in an average yearly cost of \$ [REDACTED].
- 6.50 In the estimates of use and financial analysis, the submission assumed that a response assessment would occur after the first 3 months of treatment, after which only responders would continue treatment. The response rate (69%) was drawn from the proportion of total sleep time and/or sleep latency responders at the 13-week double blind period of the NEU_CH_7911 trial. The submission assumed a treatment duration of 18 months in the financial model. The average yearly cost applied in the financial analysis is based on 100% use of an average 5.3 mg per day for 3 months, followed by 15 months of 5.3 mg per day for 69% of the cohort. This results in an average yearly cost of \$ [REDACTED].
- 6.51 Several formulations of melatonin are marketed in Australia. For example, 30 x 2 mg prolonged release melatonin (Circadin, \$32.99), 100 x 1 mg immediate release melatonin (compounded; \$45.00) and 90 x 5 mg immediate release melatonin (compounded; \$85.00) were available via the Pharmacy Direct website (accessed 9

December, 2020). Noting the arguments in the PSCR regarding comparator selection (paragraph 5.3 refers), the ESC considered that it was likely that extemporaneously compounded melatonin was being used in paediatric populations and noted the requested price was substantially higher than the private market price of compounded melatonin.

Estimated PBS usage & financial implications

- 6.52 The submission was considered by the DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impacts associated with the requested listing.

Table 13: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Rate of insomnia in ASD and other neurogenetic disorders	60%; based on a statement that paediatric insomnia has a prevalence of 50% to 75% in children with neurodevelopmental or psychiatric comorbidities (Gringras et al. 2017)	This was not the primary data source. Estimates are based on survey studies and likely to include response bias. No justification was provided for applying a 60% prevalence rate.
Insufficient response to sleep hygiene measures	75%; based on a statement that current practices recommend parent-directed behavioural sleep interventions as first-line treatment for paediatric insomnia in ASD/NGD, with reportedly a 25% response rate (Gringras et al. 2017)	This was not the primary source of this data. Success rates of behavioural interventions are highly uncertain.
Uptake rates	Yr 1: 25% Yr 2: 21.85% Yr 3: 21.76% Yr 4: 22.42% Yr 5: 25.73% Yr 6: 25.08% The submission stated that this was based on the number of eligible prescribers, however no data was provided in support of this	The method for this was not provided, and therefore could not be evaluated. No justification was provided for the pattern of uptake, nor the application of uptake rates to prevalent patients.
Script numbers	1 mg initial: ██████ ¹ scripts 1 mg continuing, first year: ██████ ¹ scripts 1 mg continuing: ██████ ¹ scripts subsequent year 5 mg initial: ██████ ¹ scripts 5 mg continuing, first year: ██████ ¹ scripts 5 mg continuing: ██████ ¹ scripts subsequent year Average scripts per year calculated for initial and continuing patients by dose, over an 18-month period. The submission assumed initiating patients would receive 3 months of treatment, after which they would be assessed for response. Responders would then receive an additional 3 months of continuing treatment in the first year, followed by 12 months of continuing treatment in the second year	Responders estimated to remain on treatment for 18 months (average duration of treatment from the trial; source not provided). The optimum duration of treatment is not yet determined, and in practice patients are likely to have a mixed pattern of use, with some remaining on treatment for a long period of time and others using intermittently The average time on treatment differs from that applied in extrapolation in economic analysis, which assumed all patients would remain on treatment until the end of the modelled time horizon (2-9 years).
Treatment responders/continuers	Continuing patients estimated to be 69% of initiating patients, based on the proportion of responders at week 13 of the NEU_CH_7911 trial.	Applying this to estimate continuing patients assumes that the response will be maintained, and that similar criteria will be used to assess response in clinical practice.

Source: Table 4.1, p.139; Table 4.2, p.140; Table 4.5, pp.141-142; Table 4.6, p.142 of the submission; Slenyto PRM Section 4 workbook
Abbreviations: ABS, Australian Bureau of Statistics; ASD, Autism Spectrum Disorders; CSR, clinical study report; DPMQ, dispensed price for maximum quantity; NGD, neurogenetic disorders; SMS, Smith-Magenis Syndrome

The redacted values correspond to the following ranges:

¹ < 500

6.53 The estimated utilisation and financial impact of listing prolonged release melatonin for the treatment of children aged 2-18 years with ASD and/or SMS, who have insomnia, is presented in Table 14 below.

Table 14: Estimation of number of treated patients and prescriptions (corrected during evaluation*)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Australian population aged between 2 and 18 years	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Eligible ASD population (2.5%)	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Eligible SMS population (0.004%)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Total eligible population	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Rate of insomnia (60%), with insufficient sleep hygiene response (75%) [45% overall]	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Uptake rate	25.00%	21.85%	21.76%	22.42%	25.73%	25.08%
Patients initiating treatment	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Initial scripts first year 1 mg (29% patients; 3.04 scripts/patient)	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Initial scripts first year 5 mg (71% patients; 3.04 scripts/patient)	█ ⁶	█ ⁷	█ ⁶	█ ⁶	█ ⁶	█ ⁶
Continuing patients at 13 weeks (69% response rate)	█ ⁵	█ ⁸	█ ⁸	█ ⁵	█ ⁵	█ ⁵
Continuing scripts first year 1 mg (29% patients; 3.04 scripts/patient)	█ ⁸	█ ⁸	█ ⁸	█ ⁸	█ ⁵	█ ⁵
Continuing scripts first year 5 mg (71% patients; 4.08 scripts/patient)	█ ⁶	█ ⁷	█ ⁷	█ ⁷	█ ⁶	█ ⁶
Continuing patients from previous year	0	█ ⁵	█ ⁸	█ ⁸	█ ⁵	█ ⁵
Continuing scripts second year 1 mg (29% patients; 12.18 scripts/patient)	0	█ ⁶	█ ⁶	█ ⁶	█ ⁶	█ ⁹
Continuing scripts second year 5 mg (71% patients; 16.29 scripts/patient)	0	█ ²	█ ²	█ ²	█ ²	█ ²
Total script volume	█ ¹⁰	█ ¹¹	█ ¹¹	█ ¹¹	█ ¹¹	█ ¹¹
Net cost to PBS/RPBS (less copayments)	\$█ ¹²	\$█ ¹³	\$█ ¹⁴	\$█ ¹⁴	\$█ ¹³	\$█ ¹³

Source: Slenyto PRM Section 4 workbook

* Corrected for error in submission. In the initial year, patients should receive 6 months of treatment (3 months of initial treatment followed by 3 months of continuing treatment for responders only). In the second year, continuing patients should all receive 12 months of treatment.

Abbreviations: ASD, autism spectrum disorders; SMS, Smith-Magenis syndrome

The redacted values correspond to the following ranges:

¹ 4,000,000 to < 6,000,000

² 100,000 to < 200,000

³ < 500

⁴ 60,000 to < 70,000

⁵ 10,000 to < 20,000

⁶ 30,000 to < 40,000

⁷ 20,000 to < 30,000

⁸ 5,000 to < 10,000

⁹ 40,000 to < 50,000

¹⁰ 80,000 to < 90,000

¹¹ 200,000 to < 300,000

¹² \$10 million to < \$20 million

¹³ \$40 million to < \$50 million

¹⁴ \$30 million to < \$40 million

6.54 The total cost to the PBS/RPBS of listing prolonged release melatonin (corrected during the evaluation) was estimated to be \$10 million to < \$20 million in Year 1,

increasing to \$40 million to < \$50 million in Year 6, and a total of \$200 million to < \$300 million over the first 6 years of listing.

- 6.55 The estimates around the size of the eligible population were poorly supported. The submission relied upon values reported in a secondary data source, mainly derived from small survey studies and prone to response bias. There was significant variability among the cited sources, particularly for the prevalence of insomnia among children with ASD and/or SMS, and the proportion of children who fail treatment with behavioural therapies or sleep hygiene training. The DUSC considered the estimated ASD prevalence rate for 2 to 18 year old children of 2.5% may be an underestimate and noted a new National Implementation Guideline Toolkit (2020) to help clinicians to upskill and deliver the recommendations in the National Guideline for the Assessment and Diagnosis of Autism Spectrum Disorders (October 2018) may increase the reported prevalence of ASD. The DUSC noted insufficient response to sleep hygiene measures was estimated in the submission to be 75% and considered this is likely an underestimate as there is no clear definition of insufficient response in the restriction.
- 6.56 The submission assumed an average duration of treatment of 18 months, based on the mean total time on treatment for patients who were prescribed melatonin during the double blind and/or open label phases (547.4 days; 1.499 years). As this was a two year trial, this duration is likely to represent the trial period, rather than duration of treatment in clinical practice.
- 6.57 The DUSC noted the treatment responders/continuers are estimated from the pivotal trial to be 69% of patients after 13 weeks. However the financial estimates apply 69% as the annual continuation rate, so the prevalent patients in Year 2 and after may be overestimated as the proportion of responders may reduce over time.
- 6.58 The submission applied a breakdown by dose of 29%, 47%, and 24% for the 2 mg, 5 mg, and 10 mg doses respectively to calculate scripts by dose. No evidence was provided to support the distribution across scripts and doses. Further, although it is not specified in the restriction, the product information specifies that the starting dose should be 2 mg. The proportion of patients commencing on a 2 mg dose should be close to 100%. Further, the 3-month treatment period applied in the financial model for initial scripts do not align with the proposed restriction, which offers 5 repeats. The dosing of prolonged release melatonin is unclear and difficult to predict, and differences in practice are likely to vary the price substantially.
- 6.59 The sponsor stated that the percentage of patients initiating treatment was estimated based on the number of eligible prescribers that are able to initiate treatment with prolonged release melatonin, which includes paediatricians, paediatric sleep physicians, paediatric neurologists, and paediatric psychiatrist. The source of the numbers for uptake was not provided in the submission, and it is unclear how they were derived. It is unclear why the numbers do not consistently increase or decrease over time. These estimates could not be verified due to poor documentation. There

was no justification for the assumed uptake pattern. It may not be appropriate to apply an uptake rate to estimated prevalence, as it does not account for patients who may have previously used melatonin. Overall, the uptake rates are highly uncertain. The DUSC considered there may be significant current use of melatonin in the ASD and SMS population and these patients will transfer to PBS subsidised melatonin, particularly if they are concessional patients. The DUSC noted an estimate of the number of these “grandfathered” patients were not included in the financial estimates. The DUSC considered the treatment uptake rate for eligible patients of approximately 25% across each of the estimate years was an underestimate due to the extent of existing private use. The DUSC considered uptake in the SMS population was likely to be closer to 100%, given the high clinical need in this population.

Quality Use of Medicines

- 6.60 The submission stated that the mini tablet formulation was particularly important for the intended treatment population, as many children with ASD have swallowing difficulties and are sensitive to smell (Malow et al., 2020).
- 6.61 The sponsor noted that they are planning on introducing a patient information booklet and a sleep and nap diary which will be given to the parents and caregivers of the patients when the patient is initiated on treatment with prolonged release melatonin. The booklet and diary will include information on the product itself, as well as a simple sleep assessment tool.
- 6.62 The DUSC noted the following quality use of medicine issues:
- The availability of PBS melatonin may lead to a reduction in the use of hypnotic drugs.
 - The consequences of long term treatment with the hormone melatonin are not known. There are uncertain effects on pubertal development and potential effects on cardiovascular, immune and metabolic systems. Ongoing monitoring is required for long term effects on sexual maturation and other systems.
 - The lack of a stopping rule in the restriction means that patients may continue longer than necessary.
 - Drug treatment for sleep problems (rather than sleep hygiene) may come to be considered normative if PBS subsidised for this indication.
 - Sleep hygiene measures are difficult to implement with children with ASD. Screen time on computers and other devices also contributes to sleep problems and may be harder to control for ASD children.
 - Some ASD patients are on stimulants which may be contributing to the sleep problems.

For more detail on PBAC’s view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of melatonin for the treatment of insomnia in children aged 2-18 years with Autism Spectrum Disorder (ASD) and/or Smith-Magenis Syndrome (SMS) where sleep hygiene measures have been insufficient. In deciding not to recommend melatonin for the requested populations, the PBAC considered the evidence presented indicated that while melatonin may be effective at increasing total sleep time (TST) for some patients, the effect was highly variable (as evidenced by the wide 95% confidence intervals) and of uncertain and likely modest clinical benefit. The PBAC considered the cost effectiveness of melatonin at the price requested in the submission could not reliably be assessed with the economic model provided. The PBAC considered the estimated number of patients likely to be treated with melatonin was poorly supported and the financial estimates were high and uncertain.
- 7.2 The PBAC acknowledged there was a clinical need for effective treatments for insomnia in patients with ASD and a very high clinical need in the SMS population. The PBAC also noted the input from SMS Australia which highlighted the impact insomnia and night time waking has on people with the condition and their carers and noted the input that melatonin is widely used in the population but is often purchased from overseas in jurisdictions where melatonin is not regulated as a pharmaceutical product. The PBAC considered there was a clinical place for a regulated pharmaceutical grade melatonin for the treatment of insomnia in patients with SMS and ASD who have failed other measures.
- 7.3 The PBAC considered the nominated comparator of standard care (comprised of behavioural measures and sleep hygiene) was reasonable. The PBAC noted there are a number of alternative formulations of melatonin available and they are likely to be commonly used in the ASD and SMS population. The PBAC noted the sponsor argued that other forms of pharmaceutical grade melatonin such as Circadin were not relevant comparators as they are not indicated for use in children and further argued in its Pre-PBAC Response that extemporaneously compounded melatonin was not a relevant comparator as it is not a modified release product. The PBAC considered that, while they may not be considered comparators (and acknowledged a comparison of effectiveness and safety would be difficult), they are substantially less costly than the price requested in the submission (paragraph 6.51).
- 7.4 The PBAC considered the requested restriction did not adequately define a population who could be eligible for PBS subsidised melatonin as no definition of failure of sleep hygiene measures (for the purposes of initial eligibility) and no definition of response to melatonin (for the purposes of continuing eligibility) were proposed.
- 7.5 The PBAC noted the submission was supported by one double blind, randomised controlled trial (NEU_CH_7911) comparing melatonin to placebo in children 2 to 18 years of age (n=125). The primary outcome of the trial was change from baseline in TST after 13 weeks as measured by sleep and nap diaries. The PBAC noted the

evaluation raised a number of issues regarding trial design that may impact on interpretation of the clinical data (discussed in paragraphs 6.6 to 6.11).

- 7.6 The PBAC noted the results of the clinical trial found an average increase in TST of 32.32 minutes per night over placebo, however also noted the wide 95% confidence interval (with a lower bound of 2.38 minutes). The PBAC was uncertain that an increase in TST of 32 minutes over placebo was clinically significant and noted the increase was not associated with significant changes in patient or carer daytime functioning as measured by most of the outcomes assessed. The PBAC noted the arguments in the pre-PBAC response that statistically significant improvements in externalising behaviour and caregivers' quality of life (on the WHO-5 scale) support the clinical relevance of the observed statistically significant differences in sleep-based endpoints. However, the PBAC was uncertain of the clinical significance of the changes observed in these two outcomes [treatment difference -0.83 (95%CI: -1.54, -0.13) for externalising behaviour and 2.17 (95% CI: 0.53, 3.82) for caregivers' well-being as measured by the WHO-5 scale]. The PBAC agreed with the ESC that sleep requirements for the age range of participants in the study (2-18 years) varies greatly and considered this further complicated interpreting the results of the study. On balance, the PBAC considered that melatonin is likely to be effective for the treatment of insomnia in the requested populations, however considered that the effect is likely to be modest.
- 7.7 The PBAC noted the submission relied on an exploratory outcome of 'responders' in the economic model, defined by either an increase in TST of 45 minutes or more per night or reduction in sleep latency of 15 minutes or more. The PBAC noted no information was provided regarding this outcome in the clinical study report and no details were provided in the submission regarding how it was analysed. The PBAC noted the percentage of responders in the melatonin arm was 68.9% and in the placebo arm was 39.3%. The PBAC noted this was likely to be largely driven by the sleep latency responders (63.8% vs 32.8% in the melatonin and placebo arms, respectively), rather than TST responders. The PBAC considered this definition of responder was of uncertain clinical significance.
- 7.8 The PBAC noted treatment with prolonged release melatonin was associated with a higher incidence of adverse events including mood swings, somnolence, and fatigue, compared with placebo. The PBAC noted there was limited safety data supporting the long-term use of melatonin in the requested populations. Although no claim was made in the submission, based on the available information the PBAC considered melatonin was likely inferior to placebo with regards to comparative safety.
- 7.9 The PBAC noted the ESC advice that the economic model provided with the submission was unreliable for decision-making (paragraph 6.47). The PBAC acknowledged the challenge of conducting a modelled cost utility analysis for melatonin based on the available clinical data. However, the PBAC considered the cost per responder model in the submission included a number of assumptions that were highly biased in favour of melatonin.

- 7.10 The PBAC agreed with the DUSC that the utilisation of melatonin was likely highly underestimated. In particular, the PBAC noted the DUSC considered that the current use of melatonin in the ASD population was likely higher than estimated and the uptake rate would be higher than estimated.
- 7.11 The PBAC considered the average dose likely to be used in clinical practice and the treatment duration were uncertain and noted the economic and financial analyses were highly sensitive to the assumed dose and treatment duration.
- 7.12 Given the very high need for effective treatments in the SMS population, the PBAC considered prolonged release melatonin may be acceptably cost-effective for this small, well-defined population at a price consistent with that of extemporaneously compounded melatonin. The PBAC advised an early re-entry pathway was acceptable **for the SMS population** if the following outstanding issues were addressed:
- A revised initial and continuing restriction criteria appropriate for the SMS population;
 - A revised estimate of the number of SMS patients likely to be treated and revised financial estimates based on (i) a rate of insomnia specific to the SMS population and (ii) an uptake rate specific to the SMS population; and
 - A requested listing based on a price consistent with extemporaneously compounded preparations of melatonin.

Resubmission via the early re-entry pathway must be lodged by week 7 of the current PBAC cycle or at the standard due date for PBAC submissions for the next cycle. If any of these terms are not acceptable to the sponsor, a standard re-entry pathway is available. The PBAC advised a standard re-entry pathway was applicable to the ASD population and should address the issues identified in this Public Summary Document (PSD).

- 7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Aspen is pleased that the PBAC has recognised a place for Slenyto in the SMS population. Aspen is looking forward to addressing the outstanding issues for the early re-entry resubmission pathway for this patient group, and working with the PBAC in the future to potentially expand the listing to include ASD patients.