

7.08 MELATONIN (PROLONGED RELEASE), Tablet 1 mg, Tablet 5 mg, Slenyto[®], Aspen Pharmacare Australia Pty Ltd.

1 Purpose

- 1.1 The early re-entry resubmission sought to address the issues raised by the PBAC in its consideration of melatonin at its March 2021 meeting.
- 1.2 In March 2021, 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. The PBAC acknowledged there was a very high clinical need for effective treatments for insomnia in the SMS population and considered 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 would be acceptable for the SMS population if a number of specific outstanding issues were addressed.
- 1.3 The resubmission requested PBS listing for the SMS population only and addressed the outstanding issues raised by PBAC as outlined in Table 1.

Table 1: Summary of key matters to be addressed for the SMS population

Matter of concern	Response	Addressed?
(paragraph 7.12) The resubmission should include a revised initial and continuing restriction appropriate for the SMS population	The re-submission included revised restrictions that defined failure of sleep hygiene by continued insomnia symptoms (defined by ICSD-3 or DSM-V criteria) for initial treatment and included definitions of response consistent with outcomes from the clinical trials.	Y
(paragraph 7.12) The resubmission should include 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) and uptake rate specific to the SMS population.	The re-submission included revised assumptions, utilisation and financial estimates specific to the SMS population. The resubmission assumed 100% of SMS patients between the ages of 2 and 18 years of would have sleep disorders and 80% would fail sleep hygiene measures and require melatonin.	Y
(paragraph 7.12) A requested listing based on a price consistent with extemporaneously compounded melatonin	The re-submission included a lower price than the March 2021 submission.	Partially

Source: Table 1.4 (p 16) (restriction); Table 4.2 (p 32) (Utilisation/financials); Table 3.1 (p 20) (Economics/pricing), paragraph references from melatonin Public Summary Document, March 2021 PBAC meeting.

2 Background

- 2.1 Melatonin was TGA registered 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 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough

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	1	60	5	\$ [REDACTED]	Slenyto® Aspen Pharmacare Australia Pty Ltd
5 mg tablet, 30	1	30	5	\$ [REDACTED]	

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 checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency
Administrative Advice: <i>No increase in the maximum number of repeats may be authorised.</i>
Administrative Advice: <i>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).</i>
Condition: Insomnia
Indication: Insomnia
Treatment Phase: Initial
Clinical criteria: Patient must have Smith-Magenis Syndrome
AND
Clinical criteria: Patient must have failed to achieve an adequate response to sleep hygiene. This should be assessed and determined based on the diagnostic criteria defined under the DSM-5 or ICSD-3 classifications. Patient has failed to get sufficient response to sleep hygiene measures
Treatment criteria: Must be treated by in consultation with a paediatrician, sleep physician, neurologist, or psychiatrist
AND
Population criteria: Patient must be aged between the ages of 2 to 18 years inclusive
Prescriber instructions: <i>For the purposes of administering this restriction, an inadequate response to sleep hygiene measures is defined as continuing insomnia as defined by either (i) in the ICSD-3 or (ii) DSM-V diagnostic criteria.</i>
Administrative note: <i>Increases up to the maximum dose as per the approved Product Information will be permitted.</i>

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 checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency
Administrative Advice: <i>No increase in the maximum number of repeats may be authorised.</i>
Administrative Advice: <i>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).</i>
Condition: Insomnia
Indication: Insomnia
Treatment Phase: Continuing
Clinical criteria:
<i>Patient must have previously received PBS-subsidised treatment with this drug for this condition. Patient must have previously received treatment with this drug</i>
AND
Clinical criteria:
<i>Patient must demonstrate a clinically meaningful response to the initial treatment Patient must have achieved a clinically meaningful response to treatment; OR Patient requires a dose adjustment (up to a maximum dose of 10 mg daily) if an inadequate response has been observed</i>
AND
Treatment criteria:
<i>Treatment must have commenced between the ages of 2 to 18 years inclusive</i>
Treatment criteria:
<i>Must be treated in consultation with a paediatrician, sleep physician, neurologist, or psychiatrist</i>
Prescriber instructions:
<i>Treatment must cease if a patient is unable to achieve a clinically meaningful response on the maximum dose of melatonin specified in the Product Information.</i>
Administrative note:
<i>Increases up to the maximum dose as per the approved Product Information will be permitted.</i>

- 3.2 The sponsor’s pre-PBAC response clarified that developmental paediatricians should also be eligible to prescribe melatonin.

For more detail on PBAC’s view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

- 4.1 There was no hearing for this item.

Consumer comments

- 4.2 The PBAC noted and welcomed the input from a health care professional and the National Aboriginal Community Controlled Health Organisation (NACCHO) via the Consumer Comments facility on the PBS website. The comments supported the PBS listing of melatonin for Aboriginal or Torres Strait Islander children.

Clinical evidence

- 4.3 The PBAC previously considered that melatonin is likely to be effective for the treatment of insomnia in the requested populations (ASD and SMS), however considered that the effect is likely to be modest (paragraph 7.6, melatonin Public Summary Document (PSD), March 2021 PBAC meeting). The PBAC previously considered melatonin was likely inferior to placebo in terms of comparative safety (paragraph 7.8, melatonin PSD, March 2021 PBAC meeting).
- 4.4 The resubmission did not provide any additional clinical evidence.

Economic analysis

- 4.5 The PBAC previously considered prolonged release melatonin may be acceptably cost-effective for the SMS population at a price consistent with that of extemporaneously compounded melatonin.
- 4.6 The resubmission stated that prolonged release melatonin (and specifically, Slenyto) provided additional benefits over immediate release (IR) compounded melatonin:
- IR melatonin only addresses sleep latency in SMS. Prolonged release melatonin improves both sleep latency and total sleep time for SMS patients. The resubmission stated this is important as patients with SMS have an inverted circadian rhythm and therefore would require a prolonged release formulation of melatonin that lasts throughout the night.
 - Slenyto is pharmaceutical grade melatonin formulated to mimic the normal physiological release of melatonin.
 - Slenyto is an age appropriate, easy to swallow, 3mm in diameter tablet (no need to crush or dissolve thereby preserving the prolonged release profile).
 - Slenyto was designed specifically for SMS patients (who often have sensory difficulties and taste sensitivities) as they are odourless, flavourless.
 - Slenyto is TGA registered, adheres to good manufacturing practices, and has a pharmacovigilance team in Australia to monitor safety (not done for compounded melatonin).
- 4.7 The resubmission stated that, based on phone calls to a number of pharmacies, the price to patients of compounded melatonin ranged from \$44.00 to \$85.00 for 100 x 1 mg capsules and \$69.00 to \$110.00 for 100 x 5 mg capsules.
- 4.8 In addition to compounded melatonin, Circadin 2 mg x 30 tablets is available for approximately \$36 and is now available over the counter (i.e., does not require a doctor's prescriptions). The PBAC noted Circadin is a TGA registered, sustained release formulation of melatonin that is indicated for insomnia in people over the age of 55 years.

- 4.9 The resubmission stated the drug cost/patient per year would be \$ [redacted] based on a monthly average cost of \$ [redacted] (assuming a daily dose of 5.3mg/day per patient, based on the clinical trials) and 12 scripts per year.
- 4.10 The PBAC noted the cost per mg of Circadin is \$0.60 to the patient, compounded melatonin ranged from \$0.15 to \$0.85 to the patient and the requested price per mg for Slenyto was \$ [redacted] to \$ [redacted] at the dispensed level.

Estimated PBS usage & financial implications

- 4.11 The resubmission used an epidemiological approach to estimate the number of patients that would be eligible for treatment (Table 2).

Table 2: Estimation of number of eligible patients

	2021	2022	2023	2024	2025	2026
Australian population	[redacted] ¹	[redacted] ¹	[redacted] ¹	[redacted] ¹	[redacted] ¹	[redacted] ¹
Prevalence of SMS	0.005%					
No. people with SMS	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²
Aged 2 to 18 year	55%					
No. people with SMS aged 2 to 18	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²
Proportion with sleep disorders	100%					
Proportion that fail sleep hygiene measures	80%					
Eligible patients	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²	[redacted] ²

SMS = Smith-Magenis Syndrome

The redacted values correspond to the following ranges:

¹ > 10,000,000

² 500 to < 5,000

- 4.12 The resubmission applied a prevalence of 0.005% to the total Australian population and then assumed 55% of these patients would be between the ages of 2 and 18 years (based on SMS Australia registry data) to estimate 500 to < 5,000 patients with SMS in Year 1. The submission considered in March 2021 applied a prevalence of SMS of 0.004% to the Australian population between 2 and 18 years of age to estimate there would be < 500 patients with SMS patients in Year 1 (Table 14, melatonin PSD, March 2021 PBAC meeting).
- 4.13 The resubmission estimated 100% of SMS patients between the ages of two and 18 years would have sleep disorders and 80% would fail sleep hygiene measures and require melatonin. The submission considered in March 2021 estimated 60% of patients would have insomnia and 75% would fail sleep hygiene measures. The estimates provided in the resubmission may be reasonable as the DUSC previously considered use in the SMS population was likely to be closer to 100% given the high clinical need (paragraph 6.59, melatonin PSD, March 2021 PBAC meeting).
- 4.14 The resubmission assumed an average treatment duration of 2 years for responding patients with an average dose of 5.3 mg per day.

4.15 The resubmission estimated a net cost to the PBS of \$0 to < \$10 million in Year 6 of listing, with a total net cost to the PBS of \$0 to < \$10 million over the first 6 years of listing.

Table 3: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	█ ¹	█ ²	█ ²	█ ²	█ ²	█ ²
Estimated financial implications						
Net cost to PBS/RPBS	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³

Source: Table 4.10 of the resubmission

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ \$0 to < \$10 million

4.16 The resubmission noted the sponsor was amenable to a Risk Sharing Arrangement (RSA) and/or Special Pricing Arrangement, to be negotiated pending the advice of the PBAC.

For more detail on PBAC’s view, see section 5 PBAC outcome.

5 PBAC outcome

5.1 The PBAC deferred making a recommendation for melatonin for the treatment of insomnia in patients with Smith-Magenis Syndrome (SMS) to allow for further consultation with the sponsor regarding a cost-effective price for melatonin. In deciding to defer making a recommendation, the PBAC affirmed its view there was a high clinical need for effective treatments for insomnia in the SMS population, however considered the requested price was unacceptably high given the availability of the Circadin brand and compounded forms of melatonin, which are substantially less costly.

5.2 The PBAC noted the resubmission presented a revised restriction for the SMS population and advised that, in addition to the changes proposed by the Secretariat in paragraph 3.1, the following amendments would be appropriate:

- The eligibility criteria should be consistent with that used in the clinical trials, rather than referring to the DSM-5 or ICSD-3 classifications: ‘Patient must have failed to achieve an adequate response to sleep hygiene and continue to experience insomnia defined as a minimum of 3 months of impaired sleep. Impaired sleep is as 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’.
- The continuation criteria should be consistent with that used in the clinical trials: ‘Patient must have achieved a clinically meaningful response to treatment defined as an increase in total sleep time (TST) of 45 minutes or more from baseline, and/or a decrease in sleep latency (SL) of 15 minutes or more from baseline’.

- Inclusion of ‘developmental paediatricians’: ‘Must be treated by a paediatrician, developmental paediatrician, sleep physician, neurologist, psychiatrist’ in the initial criteria and ‘Must be treated in consultation with a paediatrician, developmental paediatrician, sleep physician, neurologist, psychiatrist’ in the continuing criteria. The PBAC considered it may be appropriate to define ‘developmental paediatricians’ as clinicians with a membership of the Neurodevelopmental and Behavioural Paediatric Society of Australasia.
- 5.3 The PBAC noted the resubmission stated Slenyto is specifically formulated for the proposed population (paragraph 4.6 refers), however considered these factors did not justify the substantial price premium over alternative melatonin formulations. The PBAC noted that Circadin, while not specifically indicated for the proposed population, is available for a substantially lower price than was requested for Slenyto. The PBAC considered that a difference in formulation and presentation was not a sufficient reason to consider listing at a substantially higher cost than a comparable product. Overall, the PBAC considered Slenyto would be acceptably cost-effective at a price per mg of \$0.60 (at the dispensed price for maximum quantity level). The PBAC noted this was within the range of prices for compounded melatonin and consistent with the Circadin price (paragraph 4.10).
- 5.4 The PBAC advised the financial estimates should be revised, based on the following assumptions:
- A prevalence of SMS of 0.004% applied to the Australian population aged 2 to 18 years.
 - 100% of SMS patients have sleep disorders, 80% fail sleep hygiene measures and meet the restriction criteria for Slenyto. The PBAC considered it would be appropriate to assume that each patient receives, on average, 10 prescriptions per year.
 - Average dose of 5.3 mg per day.
- 5.5 The PBAC noted there is a risk of usage in patients who do not have SMS and considered an RSA would be appropriate to manage this risk.

Outcome:
Deferred

6 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.

7 Sponsor’s Comment

Aspen is pleased that the PBAC has accepted there is a clinical need for Slenyto PRM in the SMS population. Aspen is working with the PBAC/PBS pricing section to finalise the price for melatonin (Slenyto PRM) tablets.

Addendum to the July 2021 PBAC PSD:

8 Background

- 8.1 At its July 2021 meeting, the PBAC deferred making a recommendation for the listing of melatonin for the treatment of insomnia in patients with Smith-Magenis Syndrome (SMS) to allow for further consultation with the sponsor regarding a cost-effective price for melatonin. The PBAC considered melatonin would be acceptably cost-effective for this population at a dispensed price per mg of \$0.60.
- 8.2 Subsequent to the July 2021 PBAC meeting, the sponsor proposed a price for melatonin that was consistent with a price per mg of \$ [REDACTED] at the dispensed level (Table 4). The sponsor requested a Special Pricing Arrangement.

Table 4: Proposed price for melatonin

	Approved ex-manufacturer price (\$)	Dispensed price for maximum quantity (\$)	Price per mg (\$) (at the dispensed level)
Melatonin, 1 mg x 60	[REDACTED]	[REDACTED]	[REDACTED]
Melatonin, 5 mg x 30	[REDACTED]	[REDACTED]	[REDACTED]

- 8.3 The sponsor stated the prevalence assumptions for calculating the number of people with SMS aged 2 to 18 years applied in the resubmission considered at the July 2021 PBAC meeting (refer to paragraph 4.12) was appropriate and requested the PBAC reconsider the prevalence assumption in paragraph 5.4.

9 PBAC outcome

- 9.1 The PBAC recommended the listing of melatonin for the treatment of insomnia in patients with Smith-Magenis Syndrome (SMS). The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of melatonin would be acceptable in this population at the price proposed in Table 4.
- 9.2 The PBAC recalled that it had previously considered that the estimated financial impact should be based on a prevalence of 0.004% applied to the Australian population aged 2-18 years, rather than applying a prevalence of 0.005% to the total population and assuming 55% of patients are aged 2-18 years as proposed by the sponsor. However, given the uncertainty of the estimates, the minimal impact of

including the additional patients on the total financial spend (10 scripts per patient per year at an average dose of 5.3 mg, see paragraph 5.4) and the sponsor's agreement to a rebate for use exceeding the financial caps (see paragraph 4.16), the PBAC considered it would be reasonable for the financial estimates and RSA expenditure caps to be based on the sponsor's patient estimates (as outlined in Table 2). The PBAC considered a rebate of ██████% above the expenditure caps would be appropriate to manage the risk of use in patients without SMS.

- 9.3 The PBAC recommended that the Early Supply Rule should apply.
- 9.4 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for melatonin:
 - 9.5 The treatment provided a modest improvement in benefit over alternative therapies,
 - 9.6 The treatment is not expected to address a high and urgent unmet clinical need due to the availability of alternative formulations; and
 - 9.7 It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 9.8 The PBAC recommended that melatonin should not be treated as interchangeable on an individual patient basis with any other drugs.
- 9.9 The PBAC noted that this submission is not eligible for an Independent Review as it is a positive recommendation.

Outcome:

Recommended

10 Recommended listing

Add new item:

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

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 checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency
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
Treatment Phase: Initial
Clinical criteria:
Patient must have Smith-Magenis Syndrome
AND
Clinical criteria:
Patient must have failed to achieve an adequate response to sleep hygiene measures and continued to experience insomnia defined as a minimum of 3 months of impaired sleep
Treatment criteria:
Must be treated by a paediatrician, developmental paediatrician, sleep physician, neurologist, or psychiatrist
AND
Population criteria:
Patient must be aged between the ages of 2 to 18 years inclusive
Prescriber instructions:
For the purposes of administering this restriction, an impaired sleep is 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.
Administrative note:
Increases up to the maximum dose as per the approved Product Information will be permitted.

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 checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency
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
Treatment Phase: Continuing
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria: Patient must demonstrate a clinically meaningful response to the initial treatment.
AND
Treatment criteria: Treatment must have commenced between the ages of 2 to 18 years inclusive.
Treatment criteria: Must be treated in consultation with a paediatrician, developmental paediatrician, sleep physician, neurologist, or psychiatrist.
Prescriber instructions: Treatment must cease if a patient is unable to achieve a clinically meaningful response on the maximum dose of melatonin specified in the Product Information.
Prescriber instructions: A clinically meaningful response to treatment is defined as an increase in total sleep time of 45 minutes or more from baseline and/ or a decrease in sleep latency of 15 minutes or more from baseline.
Administrative note: Increases up to the maximum dose as per the approved Product Information will be permitted.

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

11 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.

12 Sponsor's Comment

Aspen is pleased with the PBAC outcome and look forward to working with the PBS to list melatonin (Slenyto PR) for the treatment of insomnia in patients with Smith-Magenis Syndrome (SMS).