

9th July 2020,

Submission: consultation to the Notice of interim decision on the proposed amendments to the Poisons Standard for melatonin

Blackmores Group understands that the interim decision relates to melatonin in modified release tablets containing up to 2mg of melatonin for the treatment of primary insomnia for adults aged 55 or over, in packs containing not more than 30 tablets.

Blackmores Group supports the interim decision made by the TGA delegate to down-schedule melatonin from Schedule 4 to Schedule 3 in the Poisons Standard, with inclusion in Appendix H.

However, we would like to submit for consideration the deletion of the age limitation of “adults aged 55 and over” for melatonin in the Poison Standard. The specific age indication is established and assessed through the product registration submission process with an evidence-based approach.

The reason for our submission is summarized below.

1. *Insomnia is a condition with no variations in prevalence by age.*

A July 2019 research surveyed 2,044 adults aged 18 years and over across Australia revealed that insomnia is a common condition amongst Australian adults.¹ Approximately more than 50% of adult Australians suffers from one or more chronic sleep symptom (eg. initiating or maintaining asleep, frequent waking) impacting their quality of life. Amongst these, 14.8% with symptoms which could result in a diagnosis of clinical insomnia.

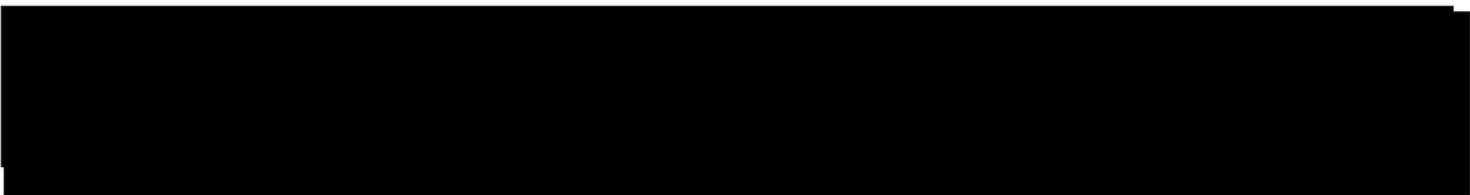
Another report estimated that 11.3% of the Australian population experience insomnia without comorbidities. Episodic insomnia is estimated to affect 20% of adults in Australia.²

2. Adults under 55 years who would benefit from melatonin as a management option for insomnia should not be denied access.

In Australia, treatments for insomnia can include:

- Benzodiazepines;
- Benzodiazepine receptor agonists;
- Dual orexin receptor agonists;
- Sedative antidepressants;
- Calcium channel alpha-2 delta ligands;
- Melatonin;
- Antihistamines.

Of the above, the sedating antihistamine (eg doxylamine) is a comparable schedule 3 over-the-counter management option for insomnia. It is noted that doxylamine is indicated for insomnia for the general “adult” population with no adult age restrictions.



3. Melatonin has a well-defined acceptable safety profile established for adults in general, the safety profile is not restricted to adults aged 55 and over.

Melatonin is available over the counter as a dietary supplement in overseas jurisdiction, is a naturally occurring hormone, produced by the brain's pineal gland.³

In Australia, melatonin is currently approved for monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 years or over.⁴

Over the years, numerous clinical trials have examined the therapeutic usefulness of melatonin in different fields of medicine with evidence suggesting a good safety profile for adults in general. The clinical applications extended beyond its traditional use as a sleep aid; into novel fields of application such as the management of jet lags, management of sleep disorders across different age groups (aged 2 to over 55 years), clinical applications in cancer therapy and in the management of adverse effects of anticancer therapy.⁵ When melatonin is used at the appropriate dose, it has been found to be well tolerated. A recent systematic review of clinical trials (aged 1-80 years) concluded melatonin has a generally favourable safety profile; the adverse events reported were generally minor, short-lived and easily managed.⁶ Melatonin is generally considered safe with short-term use in clinical studies.⁶

In comparison, to other Schedule 3 sedatives, the potential for melatonin-induced sedation is milder and less common. Melatonin appears to have a better safety profile than the existing over the counter options for insomnia and may represent a better option in preference for people who are sensitive to the anticholinergic side effects of sedating antihistamines.⁷ There was no evidence of dependence, withdrawal effects or rebound insomnia associated with melatonin use.⁸

Some of the examined clinical studies of oral melatonin supplementation in humans and the author's reported adverse events are summarised below:⁶

Papers (s)	Design	Subject	Details of melatonin dose	Safety consideration
Wilhelmsen-Langeland et al 2013 ⁹	Randomised, placebo controlled, double blind trial and open label follow-up	Generally healthy adolescents and adults aged 16-25 years with chronic sleep problems	3 mg, immediate release, once daily after 20:00 hours, 2 weeks trial	No serious side effects reported.
Hansen et al 2014 ¹⁰	Randomised, placebo controlled, double blind trial	Women aged 30-75 years undergoing breast cancer surgery, without signs of major depression	6mg once daily 1 hour before bed for 13 weeks from 1 week pre-operatively	Data suggests that melatonin is well tolerated
Sebra et al 2000 ¹¹	Randomised, placebo controlled, double blind trial	Men aged 25-55 with normal sleep pattern and normal baseline clinical parameters	10mg once daily, approximately 1 hour before bed for 28 days	The authors did not observe, according to the parameters analysed, any toxicological effect that might compromise the use

				of melatonin at a dose of 10 mg for the study duration.
Maras et al 2018 ¹²	Randomised, placebo controlled, double blind trial	Children and adolescents 2-17.5 years with autism spectrum disorder (ASD) and neurogenetic disorders (NGD) with/without attention-deficit/hyperactivity disorder comorbidity	2, 5, or 10 mg paediatric-appropriate prolonged-release melatonin for 3 months, and another 39 weeks with optional dose adjustment	The authors concluded melatonin is an efficacious and safe option for long-term treatment (up to 52 weeks reported here) of children with ASD and NGD who suffer from insomnia

With consideration of the well-established safety profile and benefits of melatonin in the general adult population across various age brackets, Blackmores Group submits that melatonin should be accessible to all adults in a similar way existing schedule 3 antihistamines are made available to adults in general for insomnia. Such that adults, regardless of age, who qualify for the appropriate use of melatonin within the approved product indication and in accordance to the supply requirements of schedule 3 is not denied this management option.

Yours faithfully



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¹<https://www.sleephealthfoundation.org.au/news/special-reports/chronic-insomnia-disorder-in-australia.html> [accessed 09.07.2020]

²https://www.apf.gov.au/Parliamentary_Business/Committees/House/Health_Aged_Care_and_Sport/SleepHealth_Awareness/Report/section?id=committees%2Freportrep%2F024220%2F26954 [accessed 09.07.2020]

³ Hawthorne. Jetlag drug remains prescription-only in Australia. Australian Medical Association. 10 February 2017. <https://ama.com.au/ausmed/jetlag-drug-remains-prescription-only-australia>

⁴ TGA. Public Summary CIRCADIN melatonin 2 mg prolonged release tablet blister pack. Australian Government Department of Health. 2019

⁵ Kostoglou-Athanassiou. Therapeutic applications of melatonin. Ther Adv Endocrinol Metab (2013) 4(1) 13–24

⁶ Foley & Steel. Adverse events associated with oral administration of melatonin: A critical systematic review of clinical evidence. Complementary Therapies in Medicine 42 (2019) 65–81

⁷ TGA. Notice of interim decisions on proposed amendments to the Poisons Standard – ACMS/ACCS/Joint ACMS-ACCS meetings. Scheduling of chemicals and poisons. 1.3. Melatonin. 10 June 2020



⁸ Chaplin & Nutt. Melatonin (Circadin): A novel hypnotic for use in older patients. Prescribed 19 October 2008

⁹ Wilhelmsen-Langeland et al. A Randomized Controlled Trial with Bright Light and Melatonin for the Treatment of Delayed Sleep Phase Disorder: Effects on Subjective and Objective Sleepiness and Cognitive Function. JOURNAL OF BIOLOGICAL RHYTHMS, Vol. 28 No. 5, October 2013 306-321

¹⁰ Hansen et al. Effect of melatonin on depressive symptoms and anxiety in patients undergoing breast cancer surgery: a randomized, double-blind, placebo-controlled trial. Breast Cancer Res Treat (2014) 145:683–695.

¹¹ Sebra et al. Randomized, double-blind clinical trial, controlled with placebo, of the toxicology of chronic melatonin treatment

¹² Maras et al. Long-Term Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children with Autism Spectrum Disorder. JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY Volume 28, Number 10, 2018