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Submission on the proposed amendments to the Poisons Standard to be considered at the Advisory Committee on Medicines Scheduling (ACMS) meeting in March 2020. Item 1.7, melatonin.

Ref. [redacted] melatonin 2 mg prolonged release tablet blister pack AUST R [redacted]

The following down-scheduling has been proposed:

That melatonin moves from schedule four (S4) to schedule three (S3) for "MELATONIN in modified release formulations up to 2 mg for human use when supplied under the requirements of Appendix M."

The proposed requirements of Appendix M are as follows: "MELATONIN - The pharmacist will record the supply of this medicine in their dispensary software, and include the patient's name, address, date of birth and gender. The pharmacist will label product with patient's name and directions for use and date of supply. The pharmacist will upload a record of supply to the patient's My Health Record."

Aspen Pharmacare Australia Pty Ltd (Distributor) strongly opposes this application.

The committee previously correctly had a great number of concerns when considering a down-scheduling of melatonin. These included misuse, inadvertent excessive or inappropriate intake of melatonin, potential for underlying conditions being undiagnosed or not managed properly, potential for interaction, use in children, lack of chronic use data, and the fact that melatonin is a potent hormone with significant effects on body systems at relatively small doses.[1] We do not believe these concerns have been resolved with this application.

Considering the criteria of Section 52E of the Therapeutic Goods Act, we are concerned about the risks and benefits of use of this medicine as a schedule 3 medicine; the potential for abuse; risks of use outside of the approved indications; and the purpose for use (primary insomnia) which needs medical management. We have further concerns also. All of these concerns are outlined below.

1. Melatonin is a medicine and not a dietary supplement. As a hormone, melatonin has a wide range of pharmacological actions in the body, not simply managing sleep.[2] Melatonin acts at MT1 receptors which are found in the pituitary, the hypothalamus, cortex, thalamus, substantia nigra, nucleus accumbens, amygdala, hippocampus, cerebellum, cornea and retina. Melatonin receptors are also found in peripheral tissues including the heart, adrenal gland, kidney, lung, liver, gallbladder, intestine, ovaries, uterus, breast, and prostate.

   Melatonin may be involved in early fetal development. The effects on circadian rhythms affect many parts of the body, e.g. affecting cortisol and insulin secretion to prepare the body for the start of the day. It stimulates the production of cytokines (specifically

interleukins) and affects T-helper immune responses. It stimulates bone cell proliferation and inhibits bone resorption.

It has important interactions (e.g. 17-fold increase with fluvoxamine use), and precautions (e.g. use in autoimmune disease).[3]

2. In the US where there is no prescription requirement, melatonin use in children has increased dramatically – five-fold between 2007 and 2012.[4] This is not just a US phenomenon as it is also evident in other countries where melatonin is available as a prescription medicine and a food supplement. In the Netherlands, where melatonin is available without prescription, researchers found, with considerable concern, that 6% of children used it at least once a week.[5] This melatonin use in children is likely to be largely driven by parental use without medical advice, and social media. A US paediatrician in 2012 noted: "Melatonin has become a mainstay of parenting in certain communities in recent years."[6]

   We believe that a down-scheduling will see Australian parents looking further to melatonin as an easy fix. This may be particularly the case in children with neurodevelopmental disorders or autistic spectrum disorders who need to be managed by an appropriate medical doctor. If down-scheduled, a pharmacist would not have adequate medical training to assess the underlying reason for co-morbidities, especially in the case of children with neurodevelopmental disorders.

   The approved product information for [redacted][3] states: [redacted] is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy. Others have also acknowledged insufficient safety data on long-term use in children.[5-7]

   There is no indication in the proposal provided regarding Appendix M as to how this would be managed, or whether use in children would even be communicated to pharmacists as off-label and not permitted. Even if communicated, collecting the patient's date of birth is insufficient as people would quickly learn to get someone else to purchase it on their behalf if supply was denied.

   If this medicine is down-scheduled to schedule 3 there will be increased use in children without a doctor's involvement. This would be misuse of the medicine, as this is not a licensed indication, and it has unknown consequences of regular or long-term use in children who are growing, developing, having changing hormones and may be going through puberty.

3. [redacted] is only approved for short-term treatment in people 55 years and over, and only for 13 weeks. Rescheduling is likely to result in off-licence use in adults younger than 55 years (children have been noted above) and for longer than 13 weeks, without appropriate medical oversight.

4. [redacted] is only approved for primary insomnia, so underlying conditions need to be ruled out. We are particularly concerned about underlying causes such as depression, alcohol abuse, anxiety, and sleep apnoea being undiagnosed and not managed appropriately should

a person get melatonin from the pharmacist. Therefore, we believe a general practitioner or sleep specialist is best to manage insomnia with melatonin. Diagnosis and management of insomnia by a pharmacist would require additional training to screen for possible underlying conditions, patient education in sleep hygiene measures and appropriate referral to medical care. This would be very time-consuming (long pharmacy consultation), and we do not believe a busy retail pharmacy will have the time available to spend with each person requesting melatonin, particularly in the discounting environment that is increasingly seen in the Australian pharmacy landscape.

5. While New Zealand has down-scheduled melatonin, this is very recent and there is no evidence from New Zealand as yet that such requirements are adhered to, prevent inappropriate supply, or result in appropriate referral. The proposal for Australia appears to differ from the New Zealand down-scheduling, and appears to have fewer safeguards. However, as noted above, these safeguards would take time, and it is unclear whether pharmacists would spend the time. In New Zealand, there is an additional schedule which permits the pharmacist to dispense a prescription medicine provided they have completed the required training and accreditation program. There is no such provision in Australia for this level of pharmacist accreditation in order to dispense a prescription medicine.

6. A down-scheduling will see sales of unregistered compounded medicines with insufficient evidence of quality, efficacy and safety. There is variability in compounded melatonin, in both the active and in the formulation, and the quality of the dose and batch variability is not assessed.

7. The ACMS and Delegate will be very mindful of the experience of codeine. Despite upscheduling to Schedule 3, increasing awareness of the codeine misuse in pharmacy, and limiting pack sizes, people misusing codeine could still access it and ultimately Australia upscheduled codeine to Schedule 4. We see parallels would be likely where a determined group of people (parents of children) will be wanting a medicine which is available without prescription, and are seeking to find ways to achieve this, including asking for off-label dispensing of melatonin 2mg tablets.

8. While some medicines are already available for insomnia, these are in small pack sizes and intended to be very short-term. Someone with longer-standing insomnia is more appropriately managed by their doctor.

While Appendix M is to be commended, it has not yet been trialed, and melatonin is not the appropriate medicine to use for a trial of this, given the concerns expressed above.

Yours sincerely,

[redacted]

References:
(Full clinical papers available on request)

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7. Efron D, Lycett K, Sciberras E. Use of sleep medication in children with ADHD. Sleep Med 2014;15(4):472-5.