Circadin® Reclassification Application

Aspen Pharma Pty Ltd

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Application for Reclassification of Circadin®

Executive Summary

This application is seeking the reclassification of melatonin in prolonged release 2 mg oral dose form to Prescription Medicine except when supplied in approved manufacturer's packs by a pharmacist who has undergone specified training on insomnia.

Circadin® (melatonin 2 mg prolonged release) was approved in New Zealand (NZ) in 2011, as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 years or over. There are no other registered medicines in NZ containing melatonin.

The reclassification of Circadin® will provide specially trained pharmacists with the ability to provide an evidence-based treatment for people 55 years and over with primary insomnia with a treatment period of up to 13 weeks. Circadin® has an acceptable tolerability, with no dependence or withdrawal effects.[1] Pharmacists will be provided with a screening tool to assess patients with insomnia for possible underlying conditions such as obstructive sleep apnoea and depression, so the pharmacist can refer the patient to the general practitioner (GP) where necessary. Pharmacists will provide patients with information on sleep hygiene and cognitive behavioural techniques for insomnia.

HISTORY

Circadin® (prolonged release melatonin 2 mg) has been available in New Zealand (NZ) since 2012, and in other jurisdictions since 2007. An application for a reclassification was submitted for the Medicines Classification Committee (MCC) meeting in May 2012, and again in October 2012. Further clarification was provided by the MCC at the May 2013 meeting.

The clear messages in 2012 and 2013 from the MCC were:

- a need for a longer time in the market and more safety data;
- work around the diagnosis of primary insomnia (including a validated screening tool);
- concern about secondary causes of insomnia;
- concern about off-label use in children, or use longer than 13 weeks;
- appropriate advice for the patient

In April 2018, the MCC considered making melatonin more available following an application from a member of the public. The committee considered melatonin was a medicine and not a dietary supplement. They agreed that melatonin has a good safety profile that may support a reclassification, and recommended reconsultation for reclassification to a restricted medicine.

We have proposed an alternative to restricted medicine, ‘prescription except when’ with certain requirements, e.g. pharmacists having additional training, and the product being supplied in an approved manufacturer’s pack that has been consented.

The proposed reclassification maximises the benefits, including the ability for pharmacists to screen for possible underlying conditions and refer for medical care where appropriate, aiding timely review by a doctor. It minimises the potential risks, e.g. of parents medicating children without medical oversight, of sales of unregistered medicines, of sales of products with insufficient proof of efficacy, and of usage by someone who needs medical review.

The reclassification of Circadin® will result in a pharmacist consultation and lifestyle advice, and (where appropriate) short-term evidence-based treatment of patients 55 years and over with primary insomnia, or referral to a doctor where indicated.

Part A

1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine

Melatonin

2. Proprietary name(s)

Circadin®

3. Name of company/organisation/individual requesting reclassification

Aspen Pharma Pty Ltd

4. Dose form(s) and strength(s) for which a change is sought

Prolonged release dose forms containing 2 mg.

This is the only registered medicine containing melatonin, and the only melatonin product with a licensed indication.

5. Pack size and other qualifications

Pack of up to 30 tablets

6. Indications for which change is sought

Monotherapy for the short-term treatment of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over.

7. Present classification of medicine

Melatonin is currently a Prescription Medicine in NZ.

In the 1990s melatonin became available on the NZ market as a supplement, and in 1996, at the 16th meeting of the MCC, melatonin was recommended to be classified as a prescription medicine.[2] Concerns outlined at this meeting 20 years ago primarily focused on lack of confidence in safety and manufacturing quality, and lack of dosing information. This has been resolved in the Circadin® formulation following research, development and registration. Concerns have not been resolved for the supplements that are being supplied on a named patient basis under section 29 of the Medicines Act.

8. Classification sought

Prescription except when: provided at a strength of 2 mg prolonged release to people who meet the clinical and eligibility criteria of the Pharmacy Council and the Pharmaceutical Society of New Zealand approved training programme on melatonin,

when sold in the manufacturer's original pack that has received the consent of the Minister or Director-General to their distribution as medicines, by a registered pharmacist who has successfully completed the approved training programme.

We have included the strength and form reflecting the only melatonin product which has sufficient proof of efficacy to meet the standards required for registration as a medicine. Efficacy data for the Circadin® 2 mg prolonged release tablet allows a risk-benefit analysis for pharmacist-supply. Evidence for unregistered section 29 melatonin preparations is inadequate.[3] There is a precedent for including the requirement of modified release, as per the classification entries for guaiphenesin.

We have been very specific in seeking a 'prescription except when' classification for two reasons:

1. The Circadin pack is shared between Australia and NZ. For a small market it is not commercially viable to require NZ-specific packaging, and stock availability and pricing to consumers may be affected. The precedent for this is with calcipotriol, Dukoral and vaccines where prescription except when was also used.

2. To reduce the risk of supply of unregistered melatonin through on-line overseas purchase. Similar reasoning was used for sildenafil regarding potential overseas purchase.

   If the medicine changed to pharmacist-only status rather than prescription except when, it is our understanding that this would potentially allow availability of unregulated melatonin from overseas into New Zealand without the checks and referrals of a qualified health professional who can refer patients on to the doctor as necessary. The committee's concerns about use in children, or someone with an underlying condition such as depression, for example, are particularly pertinent in considering this possibility.

   Allowing on-line purchase will encourage use of products that have not met the NZ safety standards for medicines. As BPAC reports[4]: *"the original source, quality, safety and efficacy of medicines purchased online cannot be verified or guaranteed."* Melatonin products in the US[5] and Canada[6] have been found to include undeclared medicines, contaminants such as arsenic, or considerable differences in strength from that specified on the label. This is reflective of the reasons for the move in NZ to prescription status in 1996, prompted by concerns about unregulated products.

We have not included the indication, dose, duration or minimum age in the above classification statements as these are specified in the current licensed indication and dosing for Circadin® which the pharmacists would need to adhere to.

The requirement for the consented manufacturer's original pack follows the wording of ethinyloestradiol for use in oral contraceptives able to be supplied by specially trained pharmacists. This part of the statement makes it very clear to pharmacists (along with the 2 mg prolonged release requirement) that the only melatonin that can

be supplied is the registered medicine. While Section 29 of the Medicines Act 1981 only allows for a medical practitioner to prescribe unregistered medicines, being very clear in the gazette notice that only the registered form is able to be supplied will help to ensure this occurs, minimising compliance issues for Medicines Control staff.

The training requirement is to maximise the benefit-risk equation.

We believe that the gazette statement listed above will resolve the questions previously raised by the committee, and ensure pharmacists have a good understanding of their responsibilities with this medicine. The proposed statement will also ensure pharmacists are well-equipped to refer people appropriately, educate patients appropriately, document consultations appropriately, and make this reclassification work well for healthcare consumers.

9. Classification status in other countries (especially Australia, UK, USA, Canada)

Melatonin is available in the US as a dietary supplement.

Melatonin is prescription-only in the UK and Australia.

In Canada, melatonin is approved as a medicinal ingredient or non-medicinal ingredient in natural health products.

10. Extent of usage in New Zealand and elsewhere (e.g. sales volumes) and dates of original consent to distribute

Sales volumes are provided in the confidential appendix.

The original consent to distribute Circadin® tablets in NZ was June 2011.

11. Labelling or draft labelling for the proposed new presentation(s)

There is no change to labelling as the product would remain prescription only. See current labelling attached (Appendix 2).

12. Proposed warning statements if applicable

The Consumer Medicine Information (CMI) which contains warning statements will be in each pack. See Appendix 3.

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

No other registered products containing melatonin are available on the NZ market. Unregistered section 29 melatonin will not be affected by this change.

Part B

Reasons for requesting classification change including benefit-risk analysis

1. A statement of the benefits to both the consumer and to the public expected from the proposed change

Insomnia is a debilitating condition with negative effects on health and quality of life.[7] Many insomnia patients do not discuss their insomnia with their doctor.[8]

Key benefits

Benefits include the following:

- Circadin® is a proven treatment for insomnia.
- patients with insomnia presenting to pharmacy can be screened for other attributable causes for their insomnia
- patients gain greater access to evidence-based screening and sleep hygiene advice
- patients can be referred to their GP for further advice and treatment to help their insomnia and any underlying conditions
- patients over 55 years old who meet the criteria can try a treatment course of Circadin® for up to 13 weeks when appropriate, at the patient's convenience

We expect to see increased referrals from pharmacists to GPs and sleep specialists from several groups of patients with insomnia:

- experiencing insomnia with other co-morbidities or long-term conditions
- experiencing insomnia concomitant to possible anxiety, depression or other underlying causes
- under 55 years with insomnia

Information about insomnia

Insomnia is common in all ages, but particularly common in older people.[8, 9] Insomnia includes difficulty falling asleep, maintaining sleep or poor quality of sleep, resulting in impaired daytime functioning. Primary insomnia is where there are no other apparent underlying causes of the insomnia, such as medical conditions.

The natural rate of remission in chronic insomnia was found to be only 13% after four months in one study,[9] thus there is a clear need for effective treatment options.

For people 55 years and over with primary insomnia, pharmacist-supply of Circadin® provides a proven short-term treatment to help get them back into a good pattern of sleep, and have improved quality of sleep and daytime functioning. Circadin® has evidence of efficacy in clinical trials,[1, 10-12] meeting the requirements of medicines regulators in NZ, Australia and Europe. Furthermore, Circadin® does not cause

dependence, withdrawal, tolerance, rebound or cognitive dysfunction, and it has a good safety profile.[1, 13]

For people 55 years and over with likely secondary insomnia, the proposed model of care will enable identification of indicators of underlying concern. This will result in referral to the GP or sleep specialist for diagnosis and management. Some people who will be screened may never have consulted their doctor regarding their insomnia.

A third group of people who will benefit from this reclassification will be people with poor sleep hygiene in either of the above groups, or in other groups, e.g. adults under 55 years who are not eligible for Circadin®. Aided by the additional training, pharmacists will be able to discuss realistic expectations of sleep quantity and quality, and provide information on CBT, or refer to the patient's GP or sleep specialist.

An important benefit is the potential to improve sleep patterns without needing to resort to prescribed benzodiazepines or zopiclone. In NZ, long-term use of such medicines is common,[14] despite the lack of support for such use. It is very likely that availability of Circadin® through the pharmacist will reduce the numbers of people who seek traditional sleeping tablets (i.e. benzodiazepines or zopiclone) through the doctor. Sleep hygiene will be discussed, allowing resolution of certain factors that may be affecting sleep.

Circadin®

Circadin® availability through specially trained pharmacists without a prescription will provide an effective treatment for primary insomnia in adults over 55 years. It has been registered throughout Europe, Australia, New Zealand, and many other countries, as a medicine proven in primary insomnia.

Circadin® contains 2 mg prolonged release melatonin. It is designed to emulate the body's secretion of melatonin, thus providing a chronobiotic action. It both facilitates sleep and shifts the sleep phase.[15]

Melatonin has a very short half-life of 20-30 minutes. However, the prolonged release Circadin® simulates the normal endogenous profile of melatonin. It peaks after 2.5 hours of intake, at about a quarter of the level of an immediate release product and lasts at least three times longer than an immediate release melatonin – for 8-10 hours,[11] declining to baseline in 10 hours.

The elderly have lower melatonin levels, and such depletion has been associated with insomnia.[16, 17] They also tend to have more transient arousals during sleep.[17] Circadin® is a synthetically made melatonin, chemically identical to endogenous melatonin, and has been proven to improve quality of sleep, morning alertness and quality of life, and reduce sleep time latency in the 55 year and older age group.[1, 12, 18, 19] Response to Circadin® is higher in those with low nocturnal melatonin production.[16]

Circadin® does not work as a classic sedative, which is part of why it lacks negative effects on cognitive function and drowsiness the next day compared

with sedatives. Instead it works to synchronise the biologic clock to work on a 24-hour cycle.

The British Association for Psychopharmacology guidelines on insomnia[15] notes that "prolonged release melatonin improves sleep onset latency and quality in patients over 55."

The data sheet[1] summarises pivotal clinical trials demonstrating faster onset of sleep by 9-11 minutes, improved quality of sleep, morning alertness and quality of life, and significantly reduced number of awakenings versus placebo. The data sheet extract is included below (indented).

> Three Phase 3 studies and a sleep laboratory study were considered pivotal. These studies enrolled patients with primary insomnia who were aged at least 55 years. Patients suffering from severe neurological, psychiatric or neurosurgical diseases or taking CNS medications including benzodiazepines or other hypnotic agents were excluded.
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> The primary assessment tool was the Leeds Sleep Evaluation Questionnaire (LSEQ), comprising 10 self-rated 100 mm-line analogue questions concerning aspects of sleep and early morning behaviour. The LSEQ measures ease of getting to sleep (GTS), quality of sleep (QOS), ease of waking from sleep (AFS) and behaviour following wakefulness (BFW). The primary outcome variable in the pivotal clinical trials was QOS, or a combination on QOS and BFW, where a patient had to show a clinically relevant improvement on both QOS and BFW. Time to onset of sleep and duration of sleep were measured objectively only in a polysomnography study. Efficacy of CIRCADIN in combination with other hypnotic agents has not been assessed.
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> In a polysomnographic (PSG) study (N = 40; 20 CIRCADIN, 20 placebo) with a run-in of 2 weeks (single-blind with placebo treatment), followed by a treatment period of 3 weeks (double-blind, placebo-controlled, parallel group design) and a 3-week withdrawal period, time to onset of sleep was shortened significantly by 9 minutes compared to placebo. A statistically significant difference favouring CIRCADIN was seen for total duration of time awake prior to sleep onset (approx change from 10 to 11 minutes for CIRCADIN and from 21 to 20 minutes for placebo). There were no modifications of sleep architecture and no effect on REM sleep duration by CIRCADIN. Modifications in diurnal functioning did not occur with CIRCADIN 2 mg. CIRCADIN did not prolong the duration of sleep significantly compared to placebo.
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> In the outpatient studies patients who failed to meet the inclusion criteria at the end of the run-in period due to the instability of their disorder (16% of the total population) were not included in the efficacy analysis.
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> In an outpatient study (Neurim VII: N = 170; 82 CIRCADIN, 88 placebo) with two week run in baseline period with placebo, a randomised, double blind, placebo controlled, parallel group treatment period of 3 weeks and two week withdrawal period with placebo, the primary efficacy endpoint was Quality of Sleep (QOS). The rate of patients who showed a clinically significant

improvement in both quality of sleep and morning alertness was 47% in the CIRCADIN group as compared to 27% in the placebo group. There was a mean difference of approximately 6 mm in quality of sleep and approximately 9 mm in morning alertness, both favouring CIRCADIN compared to placebo. Sleep variables gradually returned to baseline with no rebound, no increase in adverse events and no increase in withdrawal symptoms.

In a second outpatient study (N = 334; 169 CIRCADIN, 165 placebo) with two week run in baseline period with placebo and a randomised, double blind, placebo controlled, parallel group treatment period of 3 weeks, the rate of patients who showed a clinically significant improvement in both quality of sleep and morning alertness was 26% in the CIRCADIN group as compared to 15% in the placebo group. CIRCADIN shortened patients' reported time to onset of sleep by 24.3 minutes vs 12.9 minutes with placebo. In addition, patients' self-reported quality of sleep, number of awakenings and morning alertness significantly improved with CIRCADIN compared to placebo. Quality of life was improved significantly with CIRCADIN 2 mg compared to placebo.

A third study involved more than 600 patients over 55, over 400 of whom were on CIRCADIN treatment for up to 6 months. Patients given CIRCADIN demonstrated a difference from placebo in mean change from baseline in subjective sleep latency, assessed using a sleep diary, of -7.8 minutes after 3 weeks ($p = 0.014$). Small differences in sleep latency were generally maintained over 13 weeks of placebo-controlled treatment.

The percentage of patients showing both remission of insomnia (PSQI of < 6) and a clinically relevant improvement of 10% in quality of life scores (WHO-5 index) increased from 16.7% (cf. 10.6% placebo, $p = 0.044$) at week 3 to 25.8% at week 13 (cf. 15.7% placebo, $p = 0.0006$). This study also examined the effect of CIRCADIN on sleep latency in younger subjects with primary insomnia and low excretion of melatonin. Clinically significant effects on sleep latency were not demonstrated in these patients.

A post-marketing surveillance study in Germany of over 500 patients with insomnia who were prescribed Circadin® found that 77% of patients took the treatment for three weeks or longer.[20] The rating of sleep quality by patients improved, with 7% rating 1-3 (very good, good, fair) at baseline and 77% rating their sleep quality 1-3 during treatment. The improvement in sleep quality continued after discontinuation. Sleep quality remained high at immediate withdrawal (within two days) and at late withdrawal (around two weeks). Previous hypnotic (benzodiazepine or z-drug) use was common (68%), but 78% of previous hypnotic users did not use them after the discontinuation.

The effects of Circadin® are in line with some more involved non-drug treatments. For example in a NZ study,[21] an intervention by a GP with simplified sleep restriction and sleep hygiene advice (intervention), versus sleep hygiene advice alone (control) found significant differences between the two groups. While sleep quality and insomnia severity had significant improvements in the intervention group, total sleep time declined by 7 minutes in both groups. Sleep onset latency improved by 5 minutes in the intervention group versus a worsening of 1 minute in the control group. The NNT was 4.

Patients over 55 years with primary insomnia will benefit from having ready access to a proven, registered treatment for primary insomnia in this age group, particularly a short-term treatment without withdrawal[18, 20] or adverse cognitive effects,[22] and where screening for underlying conditions, and lifestyle advice are provided.

Other prescription and non-prescription licensed medicines for insomnia are not suitable for everyone. For example, sedating antihistamines (which are Pharmacist-Only Medicines) have anticholinergic effects causing a range of contraindications, precautions and interactions.[23] As pharmacist-only medicines, the supply is monitored by a health professional, and sales in NZ are reasonably low, reflecting the importance of the pharmacist in minimising overuse and providing sleep hygiene and other advice to aid sleep in sufferers.

2. Potential risk of harm to the consumer as a result of the proposed change, and factors to mitigate this risk

Potential risks include use in people with underlying causes of their insomnia, supply of unregistered product, supply outside of the licensed indications, and use without medical advice in children. These risks are greatest without the involvement of a health professional.

These risks are managed through the supply only by trained pharmacists, use of a screening tool, retaining the product as a prescription medicine except when supplied under certain circumstances, and requiring that only the proven formulation can be supplied without a prescription.

3. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated

Diagnosis is based on self-report[15] without need for physical examination or laboratory tests, insomnia is often self-diagnosed. Home remedies such as avoiding caffeine or having a glass of milk or warm bath before bed are common knowledge.

An important aspect of treating insomnia is assessing if underlying causes are likely and addressing these. This will be highlighted in the training, which will be primarily about identifying underlying causes, and also in the screening tools for pharmacists, and communications from the NZ distributor.

4. Relevant comparative data for like compounds

Although there are no proven compounds in the same class as Circadin® available in NZ, comparison with other sleep treatments is discussed below. As with many therapeutic areas, there is no perfect medical solution to primary insomnia. There is a need for a further non-prescription option as many people may not be finding current self-management options efficacious. Additionally, tolerance can develop to some non-prescription treatments. We have included information about prescription medicines because these are so commonly used, particularly in older people.

OTC licensed medicines for sleep

Marketed sedating antihistamines for insomnia are Pharmacist-Only Medicines. Circadin® has not been compared with sedating antihistamines in studies. However, they differ in mechanism of action, and usage. Sedating antihistamines have a maximum 7-10 day usage,[23] versus 13 weeks for Circadin®.[1] Sedating antihistamines have anticholinergic effects, and important contraindications, precautions, and interactions.[7, 23] Doubts have been expressed about their efficacy in insomnia.[7] These have a limited role in insomnia. [7]

Herbal remedies for sleep

A review by the American Academy of Sleep Medicine found little evidence of benefit in insomnia for most complementary remedies.[24]

Prescription hypnotics for sleep

While benzodiazepines and "z-drugs" are often used in general practice[25] (particularly in the elderly), and are fully funded on prescription, there are drawbacks for some users. Hypnotics change sleep architecture, reducing slow wave sleep.[9] NZ data sheets for triazolam,[26] and temazepam[27] recommend short-term usage (2-4 weeks), and clinical efficacy for benzodiazepines tends to decline after 30 days of use.[7] Benzodiazepines can cause amnesia, confusion and impair co-ordination.[25] Likewise, zopiclone is not recommended for long-term use (longer than 4 weeks).[28] Withdrawal symptoms can occur with physical dependence, and there is a prolonged half-life in the elderly (7 hours).[28] These medicines are also subject to abuse and misuse, and interact with other CNS depressants including alcohol.

A BMJ published meta-analysis of short-term treatment of people over 60 years old with sedative hypnotics (benzodiazepines and "z-drugs") found a small benefit for primary insomnia.[29] The number needed to treat (NNT) for improvement in sleep quality was 13.

Tricyclic antidepressants are sometimes used for insomnia, but can have serious side effects also.[30, 31] CBT is helpful, with long-lasting effects in some people, but it is little used because of cost and limited availability of CBT therapists,[32] and not readily available to the NZ elderly population.

Circadin® has benefits in adverse event profile, tolerance and dependence compared with treatments currently licensed for insomnia in NZ. Furthermore, the ability to use Circadin® for up to 13 weeks helps the insomnia patient to get back into a normal pattern of sleep rather than with the recommended duration of use of maximum 7-10 consecutive days for sedating antihistamines,[23] and 2-4 weeks for benzodiazepines[26, 27] and zopiclone.[28] Additionally, for those who suffer from insomnia in the winter alone,[33] a period of treatment for up to 13 weeks will be helpful.

Summary

Currently available insomnia treatments (prescription and non-prescription) have disadvantages, and a further option is needed, particularly one with proven efficacy and without dependence or cognitive impairment. Furthermore, the model of care, including the screening tool, that will go with a reclassification of Circadin® (with input from pharmacists and doctors) changes the landscape to a more collaborative and informative environment with screening and referral for secondary causes of insomnia, and provision of information by the pharmacist.

5. Local data or special considerations relating to New Zealand

Melatonin was changed to prescription medicine in NZ in 1996, due in part to a concern that it had not been subjected to any pharmaceutical regulatory approval process (causing concern about quality and safety), doses available were unsupported by information, and products were making therapeutic claims.[2] These factors have been addressed with the development and research behind Circadin®.

Approximately a quarter of adults in NZ could have a chronic sleep problem (with a higher rate in Māori vs non-Māori) according to self-reports in a prevalence study in 20-59 year old people.[34] They were not asked if they had sought help on the problem.

Arroll et al[35] found that 41% of patients 16 years and over visiting one of three general practices in Auckland reported difficulty sleeping, of whom 12% (or 5% of all patients) had primary insomnia. Specific causes of insomnia included depression (50%), anxiety (48%), general health problems (43%), obstructive sleep apnoea (9%), alcohol problem (8%), or delayed sleep phase disorder (2%).

Attempts to import unregistered melatonin into NZ are common, with a 2017 report stating that 27,000 dosage units were stopped as a result of Operation PANGEA by Medsafe, seven times as many as erectile dysfunction medicines.[36] This suggests a desire to manage insomnia without seeing a doctor. Using a pharmacist to refer people to a doctor where indicated, or supply a registered, proven product is a better option.

6. Interactions with other medicines

Pharmacists are well-trained on drug interactions, and will be able to look up the latest information to check interactions. See the attached NZ-approved data sheet for interactions.[1] These are in line with interactions on other medicines that are available through specially trained pharmacists.

- Melatonin's metabolism is mainly mediated by CYP1A enzymes, so CYP1A2 inhibitors such as quinolones may increase bioavailability of melatonin, and CYP1A2 inducers (e.g. carbamazepine, cigarette smoking) may reduce bioavailability of melatonin.
- Fluvoxamine should be avoided. CYP1A2 and CYP2C19 inhibition from fluvoxamine cause considerably greater melatonin levels (12-fold higher C_{max}).

Currently in NZ fluvoxamine is not funded by Pharmac so little usage is likely, but someone may have been prescribed it overseas.

- Inhibition of metabolism of melatonin is also caused by cimetidine, oestrogens, and 5- or 8-methoxypsoralen, increasing plasma levels. The datasheet advises caution.
- Alcohol reduces the effectiveness of Circadin® on sleep and may alter release characteristics causing immediate release rather than prolonged release.
- Circadin® may enhance sedative properties of benzodiazepines and z-drug hypnotics. Concomitant administration with zolpidem increased impairment of attention, memory and co-ordination compared with zolpidem alone.
- Co-administration with thioridazine increased feelings of muzzy-headedness compared with thioridazine alone, and with imipramine increased feelings of tranquillity and difficulty performing tasks compared with imipramine alone. Neither case had a clinically significant pharmacokinetic interaction.

7. Contraindications and precautions

Contraindications[1]

Contraindications in the data sheet are limited to known hypersensitivity to any ingredient.[1]

Precautions[1]

Circadin® may cause drowsiness, so should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety.

Circadin® has negligible influence on the ability to drive and use machines. Patients should avoid engaging in hazardous activities, such as driving or operating machinery, after taking Circadin®.

Circadin® is not recommended for use in autoimmune diseases as there is no clinical data in this population.

Circadin® tablets contain lactose.

Pregnancy and lactation

The minimum age of 55 years precludes use in pregnant women. However, in the unlikely event that this medicine is somehow used by a pregnant woman, the data sheet notes melatonin is category B3 in pregnancy.[1]

> *"No significant effects on embryofoetal development were observed in rats given oral melatonin during the period of organogenesis at doses over 900 - fold the recommended clinical dose, based on body surface area."*
>
> *"No clinical data on exposed pregnancies are available. In view of the lack of clinical data, use in pregnant women and by women intended to become pregnant is not recommended."*

8. Possible resistance

Not applicable

9. Adverse events - nature, frequency etc.

Lyseng-Williamson in 2013 stated that: "Melatonin PR 2 mg [Circadin®] has a tolerability profile that is similar to that of placebo, and is not associated with dependence, tolerance, rebound insomnia, withdrawal symptoms or any effects on psychomotor functions, memory recall or driving skills."[37]

Circadin® does not modify sleep architecture or affect REM sleep duration.[1]

Circadin® data

As reported in the data sheet, the most common adverse events for Circadin® in clinical trials were: headache, nasopharyngitis, back pain and arthalgia. These were rated common (i.e. 1%-10% of users) in both the Circadin® and placebo treated groups.[1] In clinical trials, adverse events were reported by 49% of patients taking Circadin® versus 38% taking placebo. Adverse events caused discontinuation in 2.9% of the Circadin® patients across the studies versus 4.0% of the placebo recipients. Adverse events reported in at least 1% of participants in clinical studies are listed in the table below. See the Circadin® data sheet for less common reactions.

Table 2 Overall Adverse Experience for adverse events occurring with a frequency ≥ 1%

Body System/Adverse Experience	Circadin® % (N=1931)	Placebo % (N=1642)
Gastrointestinal disorders		
Abdominal Pain	1.1	0.7
Abdominal Pain Upper	1.0	1.2
Constipation	1.2	0.9
Diarrhoea	3.1	1.8
Nausea	1.8	1.7
Vomiting	1.5	0.9
General Disorders and administration site conditions		
Asthenia	1.9	1.2
Infections and infestations		
Influenza	1.5	0.9
Lower respiratory tract infection	1.9	1.2
Nasopharyngitis	4.0	3.0
Pharyngitis	1.9	1.2
Upper respiratory tract infection	2.9	1.2
Urinary tract infection	2.1	0.7
Musculoskeletal and connective tissue disorder		
Arthralgia	3.5	1.8
Back Pain	3.8	1.5
Muscle cramp	1.1	0.6
Neck pain	1.1	0.6
Pain in extremity	1.6	1.1
Nervous system disorders		

Dizziness	1.6	1.2
Headache	5.7	6.2
Migraine	1.1	1.2
Psychiatric disorders		
Anxiety	1.0	1.2
Respiratory, thoracic and mediastinal disorders		
Cough	2.2	1.3
Pharyngolaryngeal pain	1.5	0.9
Rhinitis	1.1	0.9

Source: Circadin® data sheet 2016

The safety profile during 3 weeks and 26 week treatment periods in studies was comparable to placebo with no withdrawal and rebound effects.[1] No tolerance, rebound, or withdrawal effects were reported in an open study of 12 months' treatment with Circadin® in 96 patients.[1]

The most recent periodic safety update report (PSUR) is attached.

Pharmacist-supply

Circadin® is registered for up to 13 weeks' treatment. This will be reinforced by the company and in the training. Pharmacists have taken their responsibilities seriously in NZ when supplying trimethoprim and oseltamivir.[38, 39] However, some indicated confusion with sildenafil.[40] A key aspect of this reclassification is ensuring pharmacists have clear instructions in the gazettal, hence the wording we have proposed, and are well-informed from the start by the company and pharmacy organisations as to what they can supply and to whom. We will be encouraging the pharmacy organisations to reinforce the training instructions through reiterating key aspects of the model. Pharmacists manage maximum durations on a regular basis, e.g. with sedating antihistamines used for up to 7-10 days. Circadin® has no dependence, withdrawal or rebound effect, and after stopping treatment sleep variables gradually return to baseline.[1] Pharmacists will also be reminded about sleep hygiene and other matters that may also improve sleep. Supplies will be recorded, which helps to support the monitoring of the 13-week maximum.

In summary, safety is compatible with non-prescription usage for adults 55 years and over. Short-term safety is clearly appropriate for non-prescription use. Long-term safety has been assessed in a one-year study and several six-month studies.

Additionally, patients will be advised by pharmacists that use is for a maximum of 13 weeks. This advice will be provided on commencement of treatment, on re-supply at 4 weeks and 8 weeks, and then if seeking at the 13-week period they will be reminded to stop taking Circadin® at that time. Should the patient want to restart soon after stopping, he/she will be referred to the doctor for review.

10. Potential for abuse or misuse.

There is a potential for off-label requests from people who want the medicine outside of the licensed indication, for example for jet lag, attention deficit hyperactivity disorder

or for a person under 55 years with insomnia. This is best managed with the requirement for training and use of the screening tool. Just as pharmacists refused inappropriate requests for oseltamivir,[38] pharmacists will be able to manage this as well. We will emphasise this in communications to pharmacists, and we will ask pharmacy organisations in NZ to emphasise this to their members. We will also suggest that Pharmacy Today reiterate these key points in their coverage of a reclassification (as they have been very happy to do previously). It will be made clear that use by people under 55 years or for indications other than primary insomnia are not within the licensed indications and therefore such supplies cannot occur under this model. If a person requests the medicine outside of this indication, pharmacists can refer to the doctor for management, use the sleep screening tool (as indicated) and/or provide sleep hygiene and information on cognitive behavioural therapy.

As discussed above, the maximum 13-week period of use will be emphasised in multiple ways. It will be suggested that this is brought up at each supply (given the purchase is in a 30 tablet pack), so the patient is aware that usage will cease by the 13-week point. A desire for continuation after 13 weeks will lead to a reiteration of the short-term usage, reminders of sleep hygiene, and GP referral for review of insomnia therapy needs. When stopping the medication, there is no withdrawal and sleep variables gradually return to baseline.[11] Furthermore, stopping will save the consumer the cost of the medicine. Thus the consumer will have no difficulty stopping at the 13-week point.

It was previously suggested that adults might get Circadin® for children's use. Under the proposed model this is unlikely given the inability to pick it off the shelf or have someone under 55 years of age purchase it. There will be an extended consultation with a pharmacist, that we would anticipate would incur a cost. With free GP visits for children under 13 years-old, there is a financial disincentive to go to the pharmacy.

All of these concerns would be greater with internet access where it is likely that no healthcare professional is involved.

11. Other information

Sleep hygiene and CBT

Our model would see the pharmacist training including information on sleep hygiene and CBT that will enable discussions on these topics with patients.

How much Circadin® will be supplied?

We have proposed a model in which the pharmacist undergoes additional training and uses a screening tool.

Screening will reveal signs of possible underlying causes of insomnia that need GP referral (taking them out of the picture for potential Circadin® use). We anticipate that our model will see more referrals than Circadin® supplies. Anyone who is under 55

years is ineligible for the medicine. A discussion on sleep hygiene and CBT may reveal no further need for Circadin®.

Like other management techniques, Circadin® is not effective in all patients. Pharmacists will advise patients of this so the patient can consult their doctor if they find no benefit. For this purpose, a sleep diary is available. Additionally, they will all stop by 13 weeks, providing an opportunity to be medication-free. Under the strict requirements of supply, it is expected that, as for trimethoprim, uptake will be limited to where it is clearly indicated and where referral to the doctor is not necessary.

DSM diagnostic criteria

DSM has moved away from primary and secondary insomnia, in part because the relationship between insomnia and other condition is often bi-directional. However, we have continued to use the term primary insomnia for several reasons. Firstly, we need to screen out secondary causes and refer, as signs of depression, anxiety, sleep apnoea, and other possible underlying conditions need GP assessment. Secondly, this is the licensed indication in NZ, and pharmacists cannot supply outside of the licensed indication without a prescription. Only about 12-20% of people with insomnia are likely to fit the criteria for primary insomnia.[14, 35]

Melatonin

We have referred throughout this application to Circadin®. Worldwide we understand that this is the only registered melatonin product with proven efficacy in primary insomnia. All melatonin products are not equal – indeed we are not aware of any evidence that any have been proven to be bioequivalent to or be interchangeable with Circadin®. Thus, this application is only relating to Circadin®.

The quality issues concerning unregistered medicines have been highlighted above. There have been two recalls of unapproved melatonin products in recent years in NZ, a consumer-level recall this month owing to a piece of metal found in the tablet,[41] and a pharmacy-level recall of multiple batches of two variants of melatonin tablets owing to foreign matter within the tablets in 2016.[42]

Summary

A reclassification of Circadin® with the model of care developed provides pharmacists with tools and a collaborative model that maximises health benefits for the patient. Insomnia is a condition with important consequences for patients. Undiagnosed underlying conditions such as depression or obstructive sleep apnoea also have adverse health consequences. Reclassification of Circadin® will result in triage by an easily accessed health professional who has had additional training in insomnia, and who is using a screening tool based on the validated tool for NZ general practice. Pharmacists can screen patients for primary insomnia with the supply tools provided and have a system to refer patients with secondary insomnia or where appropriate to

the GP. For eligible patients with primary insomnia, Circadin® could be provided by the pharmacist when appropriate, following the provision of sleep hygiene / CBT information. Circadin® provides an evidence-based safe and efficacious treatment for insomnia that is used for a limited period, which allows an opportunity to “reset” the body clock at the same time as modified behaviours are implemented to facilitate the resolution of insomnia.

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