Melatonin Reclassification Application

Aspen Pharma Pty Limited

July 2012

Submission for Reclassification of Melatonin

Executive Summary

This application seeks the reclassification of melatonin in prolonged release 2mg oral dose form to Restricted Medicine (Pharmacist-Only Medicine). Melatonin 2mg prolonged release (CIRCADIN) is approved in NZ as monotherapy for the short term (up to 13 weeks) treatment of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over.

Melatonin is secreted during the night and helps achieve and maintain sleep. Melatonin declines in many people with increasing age, at a time when insomnia increases.[1-3] Because melatonin has a short half-life, CIRCADIN is prolonged release with a specific profile to mimic the physiological release of melatonin.

Melatonin has been available for over 15 years, particularly in the US where it is a supplement, used by 5% of the population.[4] Melatonin is classified a Prescription Medicine in Australia, NZ (since 1996) and the UK, and was reclassified from prescription only to Natural Health Product (NHP) status in Canada under the Health Canada Natural Health Products Directorate (NHPD) in 2004. In NZ, melatonin has been supplied under Section 29 of the Medicines Act since 1996.

Melatonin prolonged release 2mg (CIRCADIN) has proven benefit in facilitating onset of sleep, improving sleep quality, next day alertness and quality of life in people aged 55 years and over, with primary insomnia.[5-9] With a low risk of side effects mainly positive influence on daytime alertness and no risk of falls and amnesia,[5 6 8-10] lack of dependence, rebound insomnia [5 6] and lack of abuse, this medicine has a favourable risk-benefit profile for non-prescription supply. Contraindications, precautions and interactions are all consistent with Restricted Medicine (Pharmacist-Only Medicine) classification.

CIRCADIN is licensed for use for up to 13 weeks. When discontinuing the medicine there are no withdrawal effects and sleep variables gradually return to baseline.[6] Pharmacists will record supplies and the 13 week treatment period will be highlighted in pharmacist training, on product packaging, and in the pack insert. Patients will be encouraged to stop at the 13 weeks (if they haven't already stopped). Anyone needing CIRCADIN beyond this point will receive doctor referral for a review of their insomnia. Sedating antihistamines are available for insomnia as Pharmacist-Only Medicines, and also have a time-limit that pharmacists monitor. Pharmacists will be unable to supply CIRCADIN outside of the licensed indication. This is clearly emphasised in the training material and the algorithm for supply, and is written on the pack for the consumer and pharmacists. Moreover pharmacy organisations have agreed to highlight this fact also. Pharmacists are used to ensuring appropriate supply of medicines (including adherence to a minimum age for supply, for example

with cough-cold products, influenza treatments and immunisations), and used to turning down inappropriate requests, so this will be a normal practice for them.

Although advising on insomnia is current practice for pharmacists, training material reviewed by the Pharmaceutical Society of NZ and the Pharmacy Guild of NZ will be sent to all community pharmacies upon reclassification. Such material will include causes of insomnia, referral points, lifestyle measures (sleep hygiene), and duration of treatment. Screening tools for insomnia will help identify causes of sleep difficulties and appropriateness of CIRCADIN, and reduce the consultation time. A pack insert has been supplied that includes sleep hygiene measures, mention of underlying causes of insomnia, and reiterates appropriate supply. The Pharmacy Council requirements for Pharmacist-only medicines for chronic conditions require a thorough consultation in pharmacy, and records to be kept.

With assistance from the pharmacy organisations to ensure pharmacists are well aware of their responsibilities in supplying this product, including the licensed indications, duration of use and requirement for consultation records, and with the tools we have supplied, we expect that patients presenting to pharmacy with insomnia will be triaged and managed better than ever before, quite possibly with increased referrals to doctors.

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 Limited c/o Pharmacy Retailing (NZ) Ltd, trading as Health Care Logistics

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

Prolonged release dose forms containing up to 2mg [given the risk-benefit balance is unknown for immediate release melatonin or for higher strengths].

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 Medicines Classification Committee, melatonin was recommended to be classified as a prescription medicine.[11] Concerns outlined at this meeting 15 years ago, including lack of confidence in safety and manufacturing quality, and lack of dosing information, have been resolved with the research, development and registration of CIRCADIN.

8. Classification sought

Restricted Medicine (or Pharmacist-Only Medicine) when supplied in an approved pack, and with the qualifications below:

For oral use in prolonged release dose form containing 2mg or less.

CIRCADIN is the first and only licensed melatonin product in the world, including but not limited to NZ, Europe Australia and other countries around the globe. GMP

quality data and GCP efficacy and safety data for the 2mg prolonged release tablet allows a risk-benefit analysis. A meta-analysis of other melatonin formulations in primary sleep disorders in 2005 (not including CIRCADIN) noted the range of doses used in studies, and criticised published reports for inadequate description of content and quality of melatonin formulations and verification of doses.[12] Indeed, no immediate release melatonin formulation is approved or registered by any regulatory agency including Medsafe - efficacy data for immediate release melatonin is insufficient, GCP trials with this formulation do not exist and therefore a risk-benefit assessment of the immediate release melatonin is not possible.

We have thus suggested reclassification of the prolonged release dose form. This is consistent with previous MCC decisions, such as guaiphenesin in which the general sales classification statement includes *"...for oral use in modified release form with a maximum recommended daily dose of not more than 2.4 grams..."*.

We have not included the licensed indication in the above statement of classification sought as this is the same as the current licensed indication for CIRCADIN. Approved packaging ensures warning statements consistent with non-prescription use are included on the label, particularly the requirement not to use concomitantly with other sleep medications.

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

Melatonin is available in the US as a dietary supplement since it is a naturally occurring substance and is designated *"generally recognized as safe"* (GRAS).[13] Multiple strengths are readily available including 5mg tablets. These are marketed as a "sleep aid". According to the CVS Pharmacy Melatonin 5mg packaging: *"Melatonin is an excellent choice for people experiencing occasional sleeplessness, those experiencing jet lag, or anyone looking to improve their overall sleep quality."*

Melatonin is prescription-only in the UK, Australia and Europe.[13]

In Canada, melatonin is classified as a medicinal ingredient under the Health Canada Natural Health Products Directorate (NHPD), changing from prescription only in 2004.[13]

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

Sales volumes in NZ are unknown, given distribution has been via Section 29 of the Medicines Act, and CIRCADIN was not distributed in NZ prior to 2012. Further confidential information about international use of CIRCADIN and local sales of melatonin is available in Appendix 1.

In the US where melatonin has been considered a dietary supplement since 1994, the National Health Survey in 2002 of 31,044 people (all ages) found 5.2% reported using melatonin at least once in the previous 12 months.[4] This would equate to 15 million people in the US.

The original consent to distribute CIRCADIN tablets in NZ was June 2011. CIRCADIN received centralised approval for the EU as a prescription medicine on 29 June 2007. Distribution in parts of the EU commenced in October 2007, and in the UK in June 2008. In Australia, following approval in December 2009, CIRCADIN was distributed from March 2010. CIRCADIN has been distributed in NZ from February 2012.

CIRCADIN has been approved in 40 countries: the EU approval is for 27 countries and there are 13 other countries in which CIRCADIN is approved. An estimate of the number of daily doses of CIRCADIN since launch (29 June 2007) has been calculated from sales volumes. These data represent an estimation of patient exposure to CIRCADIN based on the number of packs sold by Neurim. It is estimated that 2,762,186 patients have been prescribed marketed CIRCADIN in all these countries.

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

Draft labelling is attached (Appendix 2).

12. Proposed warning statements if applicable

Draft labelling is attached (Appendix 2), and a pack insert will be inside each pack.

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.

Part B

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

Insomnia is a debilitating condition that negatively affects health, work performance, and quality of life.[14-17] Many insomnia patients do not discuss insomnia with their doctor.[18]

Having melatonin available through the pharmacist, using the short screening tool in pharmacy, documenting consultations for melatonin, and refreshing pharmacist knowledge, will increase triage and advising of patients with insomnia. We believe this will increase referrals of people with potential underlying causes of insomnia to GPs. Additionally, people who are currently untreated (by medication or behavioural therapy or lifestyle), or who are using unproven measures, will be able to access a medicine that has been proven to be safe and effective in insomnia patients, and be given sleep hygiene advice. Finally, we anticipate that use of melatonin and pharmacist's advice may avoid harm in two ways. Firstly, through the health benefits of improved sleep, and secondly through the avoidance (for some) of prescription hypnotics and sedatives or OTC sedating antihistamines, which are associated with important side effects.

Insomnia is common in all ages, but particularly common in older people.[15 18] Insomnia includes repeated difficulty falling asleep, getting sufficient sleep or sufficient quality of sleep resulting in daytime impairment. A quarter to a third of people over 65 years complain of insomnia.[16]

Insomnia increases risk of poor health (including psychiatric disorders,,[14] and hypertension),[15 17] and reduces work performance and attendance, and quality of life.[15 16] It adversely affects memory, concentration and relationships.[19]

The natural rate of remission in chronic insomnia was found to be 13% after four months in one study, thus there is a clear need for effective treatment options.[15] Consumers over 55 years will benefit from having ready access to a proven, licensed treatment for primary insomnia in this age group, particularly one without withdrawal, rebound[6], risk of falls[20] or adverse cognitive effects.[21]

There is no perfect solution to insomnia. Sleep hygiene alone is not effective according to some reviewers.[19 22]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] and have been associated with cognitive impairment in elderly people.[24] Additionally, doubts have been expressed about their efficacy in insomnia,[16] particularly given tolerance occurs in as little as four days.[22] Prescription hypnotics can cause dependence and tolerance, affect cognition, increase risk of falls,[16 22] and hip fractures.[25-28] A BMJ meta-analysis found benzodiazepines and z-drugs provided small benefit in people over 60 years, with a number needed to treat (NNT) of 13 .[29] Furthermore, almost all

studies of benzodiazepines and z-drugs have been conducted in short-term use situations (e.g. seven days).[30] Falloon et al. stated that *"sedatives should be used as a last resort when other approaches have failed because of risks of tolerance and adverse effects"*, Nevertheless, these medicines are growing in usage at 7% per year with 560,000 prescriptions written per year in NZ for zopiclone alone,[31] and many patients treated indefinitely.[22] A study in Australian general practice, found 82% of consultations for new cases of insomnia receive a prescription and 95% of all insomnia consultations are prescribed medicines.[32] Benzodiazepines or related drugs represent 95% of these prescriptions. Advice and counselling is given in approximately 20% of these consultations. In patients over 60 years of age, chronic benzodiazepine or z-drug use carries the risk of exacerbations of pre-existing psychomotor or cognitive impairment, which may result in an increased risk of falls, motor vehicle collisions, household accidents or confusion and memory problems. Recent studies have also pinpointed the potential increased risk of Alzheimer's disease, and mortality after chronic hypnotic drugs consumption[33 34].

Tricyclic antidepressants are sometimes used for insomnia, but can have serious side effects also.[22 30] Cognitive behavioural therapy (CBT) is helpful, with long-lasting effects in some people, but it is little used because of cost and limited availability of CBT therapists,[35] and certainly not readily available to the NZ elderly population.

Melatonin has benefits in adverse event profile, tolerance and dependence compared with treatments currently licensed for insomnia in NZ. Furthermore, the ability to use melatonin 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[36 37] and zopiclone.[38] Additionally, for those who suffer from insomnia in the winter alone,[39] a period of treatment for up to 13 weeks will be helpful.

Mode of action of melatonin

Melatonin 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 our biologic clock so we work on a 24 hour cycle.

Melatonin (N-acetyl-5-methoxytryptamine) is the primary hormone produced by the pineal gland from serotonin and provides a signal of darkness to the organism.[40]. It is an endogenous regulator of the circadian clock and a sleep promoter in humans. Plasma levels are greatest during nocturnal periods, with secretion increasing soon after the onset of darkness, peaking in the middle of the night (between 2 and 4am) and gradually reduced during the second half of the night.[41] This activity serves to define the "biological night" for humans. Lerner discovered melatonin in 1958, reporting sleepiness when he took it.[3] Taken during daytime it when the endogenous levels are low, it causes sleepiness, reduced alertness and affects cognitive performance, particularly when lying down and in dim light.

According to Brocklehurst's Textbook of Geriatric Medicine and Gerontology (7th Edition 2010):[18]

> *"The circadian rhythm itself also shows evidence of age-related fragmentation, with sleep becoming more desynchronized and likely to impinge on daytime activities. Recent research suggests that an age-related reduction in sleep promotion of the circadian pacemaker, along with decreased homeostatis pressure for sleep in older adults, may be involved in this desynchronization."*

The suprachiasmatic nuclei (or SCN) is the pacemaker for our circadian rhythm of one sleep per day in adults.[19] However, it does not operate on a 24 hour clock, but instead on a slightly longer time period (24.2 or 24.3 hours). Over time for some people this can cause desynchronisation of the person's sleep-wake cycle.[19]

The SCN is affected by light and melatonin, and these factors "*entrain*" the body to maintain a 24 hour cycle.[19] Social cues and mealtimes have a smaller entraining effect. Light indirectly influences the pineal gland through the SCN and the retino-hypothalamic projection.[3] Bright light suppresses melatonin production, dark or dim light stimulates melatonin production.[19] Absence of bright light does not stimulate melatonin production unless it is about 16 hours after the previous melatonin cycle stopped. Melatonin is secreted from about 9pm-10pm peaking around 3-5am and declining to daytime values by about 8-9am in most healthy adults,[3] but this depends on bedtime and stimulation from light.[19] Thus, without light to entrain, the sleep period gradually moves later and later. With abnormal times of light and bedtime (e.g. daytime naps) the body can become desynchronised.[19] Blind people with no light perception often have a melatonin rhythm that is not matched to daytime and night-time, and melatonin is the treatment of choice in this condition.[3] The weaker light-dark cycle in winter can change the rhythm compared with summer.[3]

The primary effects of melatonin are in the central nervous system where melatonin helps synchronise the biological clock and promotes sleep.[19] Rather than being a sedative as such, it triggers the natural process in the body. The circadian timing system controls the sleep-wake rhythm. This system is affected by a variety of stimuli including light in the retina, circadian hormones, and neurotransmitters. Long periods of light or dark (created artificially) affects the circadian timing system and affect melatonin release. In elderly insomniacs, daytime exposure to bright light increases the secretion of melatonin and improves sleep.[42] Administering melatonin helps when the circadian timing has lost synchronicity. In blind-from-birth children, melatonin normalises their chaotic circadian sleep-wake rhythm.[40] Melatonin is not a hypnotic in the classic sense, it instead works on the sleep-wake rhythm improving sleep continuity and REM sleep.

Melatonin has a very short half-life of approximately 20-40 minutes in humans, which creates a difficulty for administering the medicine in an immediate release formulation.[40] To address the therapeutic situation, a prolonged release formulation of melatonin was developed, which circumvents the fast clearance of the hormone and provides a melatonin profile in the blood more closely matched to the normal physiological release. It peaks at about a quarter of the level of the immediate release product and lasts at least three times as long as melatonin (see graph in Zisapel 2008 paper),[9] declining to baseline in 10 hours. The elderly have lower melatonin levels, and such depletion has been associated with insomnia.[1] [2] They also tend to have more transient arousals during sleep.[2] CIRCADIN is a synthetically

made melatonin, chemically identical to endogenous melatonin, and has been proven to improve sleep in the 55 year and older age group.[41] Response is higher in those with low nocturnal melatonin production.[1] The datasheet (Appendix 3) 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. CIRCADIN availability without prescription, through the pharmacist as a Pharmacist-Only Medicine provides an effective and safe treatment for primary insomnia, in adults over 55 years.

The Pharmacist-Only availability provides a health professional consultation to help rule out secondary causes of insomnia, such as depression and adverse effects of medicines.

Pharmacists already advise on insomnia, and their undergraduate training and continuing education material (e.g. recent College of Pharmacists' course, OTC Healthcare Handbook) provide information on the condition as well as sleep hygiene and other treatments. However, further training material will provide a welcome update for pharmacists in this important area. Pharmacists are familiar with melatonin, having supplied it without prescription up until 1996, and subsequently under Section 29 of the Medicines Act pursuant to a doctor's prescription. Pharmacists have always been able to supply certain sleep remedies without prescription, including chloral hydrate through the 1990s.

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

With approximately a third of the population suffering from sleep disorders intermittently, and 10% or more chronically,[15] [16] and diagnosis based on self-report without need for physical examination or laboratory tests, insomnia is readily self-diagnosed. Home remedies such as avoiding caffeine or having a glass of milk before bed are common knowledge.

An important aspect of treating insomnia (regardless of treatment) is assessing if insomnia is secondary to other causes like depression or anxiety and addressing these. This will be highlighted in training material for pharmacists (Appendix 4) and on the CIRCADIN packaging. This need already exists in the non-prescription environment, with sedating antihistamines available through pharmacists for sleep and with supplements such as valerian available "to support sleep". Additionally, as melatonin is not beneficial in secondary insomnia, the problem will not be masked, and the affected person is likely to seek further assistance.[13]

Pharmacists have had training in sleep disorders at the undergraduate stage and through continuing education (e.g. articles in the Best Practice Journal from BPAC[43] and Pharmacy Today, and a 2010 Sleep Medicine College of Pharmacists' update). History is the main diagnostic tool,[44] so appropriate questioning allows pharmacists to triage these patients, referring those where it is likely that insomnia is secondary to another cause. Additionally, lifestyle factors (including sleep hygiene) are a key component of both undergraduate training and continuing education.

We will send training material (see draft Appendix 4) to all community pharmacies upon reclassification of this medicine. This material will emphasise the need to ascertain if other causes are likely and insomnia is secondary to these (and to refer if suspected). The draft training material has incorporated advice from the Pharmaceutical Society of NZ and the Pharmacy Guild of NZ.

3. Relevant comparative data for like compounds

Although there are no compounds in the same class as melatonin, comparison with other sleep treatments is given 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 non-prescription treatments efficacious, or may have contraindications, precautions for use, interactions or side effects that may preclude their use. We have included information about prescription medicines because these are so commonly used, particularly in older people,[44] thus they are a logical comparator as well as the non-prescription options.

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.[41] Sedating antihistamines have anticholinergic effects, causing adverse events including cognitive impairment, and have some contraindications, precautions, and interactions.[16 23] A significant (200 reference) insomnia review from 2008 noted that "few data support a favourable risk-benefit ratio for antihistamines in the treatment of insomnia".[16]

Herbal remedies for sleep

Herbal remedies such as valerian are readily available without restriction in pharmacies, supermarkets and health stores to support sleep. A systematic review on valerian in 2006 found valerian "might improve sleep quality without producing side effects", but there were significant methodologic problems in most studies and evidence of publication bias.[45] Other herbals have little evidence.[45]

Prescription hypnotics for sleep

Benzodiazepines and "z-drugs" are often used in general practice[44] (particularly in the elderly). In NZ prescriptions for hypnosedatives increased 7% annually from 2002-2010.[31] Over 560,000 prescriptions of zopiclone were written in the year ending June 2010.[31] There are drawbacks for some users. All hypnotics change sleep architecture, reducing slow wave sleep.[15] NZ datasheets for triazolam,[37] and temazepam[36] recommend short-term usage (2-4 weeks), and clinical efficacy for benzodiazepines tends to decline after 30 days of use.[16] Benzodiazepines can cause amnesia, confusion and impair co-ordination.[44] Likewise, zopiclone is not recommended for long-term use (longer than 4 weeks).[38] Withdrawal symptoms can occur with physical dependence, and there is a prolonged half-life in the elderly (7

hours).[38] These medicines are also subject to abuse and misuse, and interact with other CNS depressants including alcohol. Poisonings with hypnosedatives in NZ have been increasing at around 7% per annum – similar to the increase in usage. Illicit drug use is a problem in NZ with these medicines and is predicted to increase further with the change in Pharmac funding of these medicines.[31]

A meta-analysis published in the British Medical Journal (2005) found a small benefit of short-term treatment of people over 60 years old with sedative hypnotics (benzodiazepines and "z-drugs").[29] The number needed to treat for effect was 13 (i.e. 13 needed to receive a sedative for one to have improvement in sleep quality; confidence interval 6.7-62.9), and the number needed to harm was 6 (confidence interval 4.7-6.1). Adverse events were mostly reversible and not severe. Morning or daytime fatigue were significantly more common (3.8 fold, confidence interval 1.9-7.8) with sedatives than placebo, as was impairment on performance tasks the morning after treatment.

In a double-blind, cross-over comparison of zolpidem and CIRCADIN, CIRCADIN did not impair cognitive performance, simulated driving or memory compared to placebo, but zolpidem impaired all of these significantly more than CIRCADIN.[21] For impaired memory, the effect from zolpidem remained significant the next morning.

In a randomised, double-blind, 3-way crossover, single dose, placebo-controlled study investigating the effect on postural instability of melatonin and zolpidem in healthy adult subjects aged of 55 to 64 years, negative effect of zolpidem on postural stability that is causally related to the increase in risk of falls and injuries in patients aged 55+ years was demonstrated. Circadin did not increase the risk of body sway and therefore the potential for patients to fall[20].

Summary

Pharmacists are already providing products and advice for insomnia, and self-selection of herbal remedies with no advice is possible. Currently available insomnia treatments (prescription and non-prescription) have drawbacks, and a further option is desirable, particularly one with proven efficacy and without dependence or cognitive impairment

4. 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.[11] These factors have been addressed with the development and research behind CIRCADIN.

5. Interactions with other medicines

From the NZ-approved datasheet the following interactions are possible:[41]

- 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.
- Inhibition of metabolism of melatonin is also caused by cimetidine (slight according to Stockley's)[46], oral contraceptives, and 5- or 8-methoxypsoralen, increasing plasma levels.
- 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.

Stockley's reports also:[46]

- Chronic use of melatonin modestly impairs the hypotensive effects of nifedipine, but single-time point clinic blood pressure was unchanged. Stockley's summarises: "Given the overall change was small, the clinical relevance of the effect is probably minor." Subsequent research provides reassurance in this area.[17]
- Three case reports of increased prothrombin time and three of decreased prothrombin time with co-administration of warfarin and melatonin may be idiosyncratic cases.
- Caffeine increases the bioavailability of melatonin when a 200mg dose was close to the melatonin dose. [note: given caffeine is likely to be avoided in the evening by people trying to resolve ongoing insomnia, and 200mg is substantially higher than in a cup of tea or coffee; this is probably not important].

These drug interactions are reasonable for a Pharmacist-Only Medicine. The pharmacist training material will include information on these interactions, with particular emphasis on fluvoxamine.

6. Contraindications and precautions

Contraindications in the datasheet are limited to known hypersensitivity to any ingredient.[41]

Precautions[41]

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, information from the datasheet and Briggs' Drugs in Pregnancy and Lactation is provided below.

The datasheet notes melatonin is category B3 in pregnancy.[41]

> *"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."*

The entry in Briggs' Drugs in Pregnancy and Lactation (8th Ed 2008) is summarised as follows.[47] Melatonin readily crosses the placenta. While no reports of human pregnancy with exogenous melatonin are available, use in pregnancy has probably occurred with the availability as an OTC nutritional supplement. Animal data shows lack of noticeable toxicity and structural defects, in rats during pregnancy but there were adverse effects on development of the neuroendocrine reproductive axis in female rat foetuses. Briggs noted that "There is probably no relationship of this toxicity in pregnant humans consuming occasional low (≤10 mg) doses, but high doses or frequent use during gestation should be avoided."

Both Briggs and the datasheet recommend avoidance in breast-feeding due to insufficient information.

The US CVS Pharmacy Melatonin 5mg 120 tablet pack purchased in the US in November 2011 warns: *"not intended for use by pregnant or nursing women."*

7. Possible resistance

Not applicable

8. Adverse events - nature, frequency etc.

Melatonin has been extensively studied in humans and animals for nearly 30 years. For many years melatonin has been commercially available in Europe and elsewhere as a subcutaneous implant in domestic animals to control reproduction

timing. For animals that are seasonal breeders (e.g. sheep), annually occurring changes in day length affects the phasing and duration of melatonin production which in turn affects reproduction.

Short-term use of melatonin is relatively safe,[12] [13] consistent with OTC usage. Long-term usage indicators (described below) from spontaneous reporting, studies of 6 months to 1 year, lack of US reports despite ready availability there for over 15 years, and long-term use of medicines that increase endogenous melatonin levels substantially, give no cause for concern for OTC usage.

CIRCADIN data

As reported in the datasheet, 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.[41] Adverse events caused discontinuation in 2.9% of the CIRCADIN patients across the studies versus 4.0% of the placebo recipients. The safety profile during 3 weeks and 26 week treatment periods in studies was comparable to placebo with no withdrawal and rebound effects.[41] No tolerance, rebound, or withdrawal effects were reported in an open study of 12 months treatment with CIRCADIN in 96 patients.[41] Table 1 below is from the datasheet.

Table 1 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

Please see the attached datasheet (Appendix 3) for less common adverse events (<1%).

A recent double-blind, crossover, placebo-controlled study in people with insomnia and type II diabetes mellitus found 3 weeks of CIRCADIN had “no significant effect on routine laboratory tests, glucose and lipid metabolism compared with 3 weeks of placebo.[48] The following five month open label treatment was associated with a significant improvement in HbA1c (9.13% to 8.47%). No interactions were observed with other medicines. There was no effect on C-peptide levels, suggesting a lack of effect on release of insulin in these patients. A combined analysis of studies dividing out a subpopulation of people on antihypertensives, did not find any differences

between prolonged-release melatonin and placebo in vital signs including daytime blood pressure.[17]

The two most recent periodic safety update reports (PSUR) are attached in Appendix 5.

Spontaneous reports

Given the availability of melatonin other than CIRCADIN internationally, information has also been derived from other sources. NZ's Centre for Adverse Reaction Monitoring (CARM) had received only four reports of adverse events by February 2012 (Appendix 6), all of which were graded as not serious and recovered without sequelae. The UK spontaneous reports (Drug Analysis Prints) received 91 ADR reports for melatonin (including CIRCADIN and other non-registered products) between 1963 and 25 May 2012 (first report 2001). There were six ADR reports since the previous reclassification submission (report dated 17 November 2011). Melatonin has been Prescription Medicine in the UK in this time, so usage should have been monitored by doctors. Thus, the low number of spontaneous reports from a larger population in which some longer term use was likely to have occurred is reassuring. These spontaneous reports do not indicate any particular important pattern emerging. A summary of these reports is available at: http://www.mhra.gov.uk/home/groups/public/documents/sentineldocuments/dap_1340773829097.pdf

In comparison, 1407 spontaneous adverse reaction reports (Drug Analysis Prints) were reported for zopiclone, including 18 fatalities from overdose (some of which were in combination with other agents), see:

http://www.mhra.gov.uk/home/groups/public/documents/sentineldocuments/dap_1340779694856.pdf

Other published data

A high-quality review of melatonin from 2004, commissioned by the Agency for Healthcare Research and Quality (US) reported adverse effects to be nausea (incidence ~1.5%), headache (incidence ~8%), dizziness (incidence ~4%) and drowsiness (incidence ~20%), not significantly different from placebo.[13] Melatonin appears to be a relatively safe substance when used in the short term, over a period of days or weeks, including at relatively high doses and different formulations.[13] This review noted that the safety over months and years remains unclear.[13] However, this review took place in 2004, and longer-term studies using CIRCADIN have since been published (several with six months' treatment, and one with one year of treatment).

Two case studies of long-term use (e.g. 10 years) have been published, neither of which indicated any problems.[49]

US availability

Melatonin has been readily available on the US market since the mid-1990s. For example: a melatonin 5mg pack (CVS Pharmacy) was purchased from a pharmacy

in the US in November 2011. Containing 120 5mg tablets, with a recommended dosage of one tablet per day, this contains 4 months' supply. Instructions advise to limit use to two months with a break of one week. With 5% of the US population (i.e. 15 million people) taking at least one dose in the past 12 months,[4] long-term use will have occurred in a substantial number of people.

Despite the ready availability in the US of large quantities, with some at least instructing one week off every two months, long-term problems have not appeared in the literature. A Medline search conducted in January 2012 on melatonin looking for adverse events did not reveal any cause for concern. Reactions Weekly, a publication that summarises adverse drug reaction reports in published literature has 13 entries (search conducted 23 January 2012) with the earliest in 1995, and no common theme coming through.

Other medicines increasing endogenous melatonin

Looking more laterally, some drugs that increase endogenous melatonin levels are used long-term, for example desimipramine increases melatonin levels in depressed patients and normal subjects after one day, and this is sustained over a six week period (only the depressed patients were treated for six weeks).[50] Additionally, fluvoxamine increases melatonin levels markedly through inhibition of melatonin metabolism. Fluvoxamine 100mg increased the C_{max} and AUC of naturally available (endogenous) melatonin to three times the normal level in healthy volunteers.[51] Given the long-term usage of these medicines, and the fact that both are prescription medicines, it does not appear that their usage has caused unusual safety signals different from other antidepressants with a lesser effect.

OTC usage

CIRCADIN is licensed for 13 weeks' treatment. This will be reinforced in training material. Pharmacists have been shown to take their responsibilities seriously in NZ when supplying other newly reclassified medicines available through the pharmacist.[52] Pharmacists are used to managing a maximum duration, with sedating antihistamines used for up to 7-10 days. There is no dependence, withdrawal or rebound effect, and after stopping treatment sleep variables gradually return to baseline.[41] Pharmacists will also be reminded about sleep hygiene and other behavioural measures that may also improve sleep. Should the patient require further melatonin after this 13 week period, the pharmacist will refer to the doctor for review. It is noted that many people of this age will be consulting their doctor regularly for other medical needs, so this can be done in a routine consultation. As a pharmacist-only medicine, supply 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 – showing beneficial long term safety profile. No long-term concerns have arisen from spontaneous reports to the regulator in the UK or to CARM in NZ where usage has been prescription-only (with products brought in on a named patient basis until CIRCADIN marketing in the UK in 2008). It is reasonable to expect that long-term use will have occurred in the

US, and safety signals indicating long-term problems have not been seen in published literature. Additionally, with a 13-week maximum supply period as a Pharmacist-Only Medicine, patients will be advised by pharmacists and product packaging firstly on commencement to use for a maximum of 13 weeks, and then at the 13 week period to stop taking at that time. Should the patient want to restart soon after stopping, he/she will be referred to the doctor for review. Pharmacists are used to monitoring supplies of sleeping preparations and referring to doctors as appropriate so this will be a matter of course for them.

9. Potential for abuse or misuse.

Melatonin does not provide a "high" feeling, is not used recreationally, and does not cause dependence and tolerance. Abuse is not a concern.

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. Just as in the case of oseltamivir another Pharmacist-Only Medicine, pharmacists are unable to supply oseltamivir in advance of need, and refused inappropriate requests,[52] pharmacists will be able to manage this as well. The key point will be an emphasis in all training material and we will ask pharmacy organisations in NZ i.e. the Pharmaceutical Society of NZ, the Pharmacy Guild of NZ, and Pharmacybrands to emphasise this to their members. All three organisations have indicated support in doing this. 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 as a Pharmacist-Only Medicine. If a person requests the medicine outside of this indication pharmacists can instead suggest another treatment where a suitable one exists, or refer to the doctor for further treatment options. Research on five years supply of oseltamivir suggests that NZ community pharmacists have been very responsible with this medicine.[53] If all information is communicated consistently by all parties outlined above (and supported by the pack) with a very clear message that pharmacists can only supply CIRCADIN without prescription to people 55 years and over with insomnia diagnosed by the pharmacist, for a maximum of 13 weeks following the Pharmacy Council's requirements for supplying a pharmacist-only medicine for a chronic condition, and that it is illegal to supply it otherwise, we expect pharmacists will do this very well, as they did with oseltamivir.

As discussed above, the maximum 13-week period of use will be emphasised by Aspen Pharma Pty Limited, including through the training material. It will be suggested that this is brought up at the first supply and second supply (assuming purchase is in a 30 pack), so the healthcare consumer is aware that after three months usage will cease. When stopping the medication, there is no withdrawal and sleep variables gradually return to baseline.[9] Thus the consumer will be able to stop at the 13 week point. Any desire for continuation after 13 weeks will be referred to the doctor for review of insomnia therapy needs.

References

1. Leger D, Laudon M, Zisapel N. Nocturnal 6-sulfatoxymelatonin excretion in insomnia and its relation to the response to melatonin replacement therapy. *The American Journal of Medicine* 2004;116:91-5.
2. Chokroverty S. Chapter 36 - Sleep Disorders in the Elderly. In: Chokroverty S, editor. *Sleep Disorders Medicine (Third Edition)*. Philadelphia: W.B. Saunders, 2009:606-20.
3. Arendt J. Melatonin. In: Martini L, editor. *Encyclopedia of Endocrine Diseases*: Elsevier, 2004:228-37.
4. Bliwise DL, Ansari FP. Insomnia associated with valerian and melatonin usage in the 2002 national health interview survey. *Sleep* 2007;30(7):881-4.
5. Lemoine P, Garfinkel D, Laudon M, et al. Prolonged-release melatonin for insomnia - an open-label long-term study of efficacy, safety, and withdrawal. *Ther Clin Risk Manag* 2011;7:301-11.
6. Lemoine P, Nir T, Laudon M, et al. Prolonged-release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects. *Journal of Sleep Research* 2007;16(372-80).
7. Wade AG, Ford I, Crawford G, et al. Nightly treatment of primary insomnia with prolonged release melatonin for 6 months: a randomized placebo controlled trial on age and endogenous melatonin as predictors of efficacy and safety. *BMC Med* 2010;8:51.
8. Wade AG, Ford I, Crawford G, et al. Efficacy of prolonged release melatonin in insomnia patients aged 55-80 years: quality of sleep and next-day alertness outcomes. *Curr Med Res Opin* 2007;23(10):2597-605.
9. Zisapel N, Lemoine P. Efficacy and Safety of Circadin in the Treatment of Primary Insomnia. *US Neurology* 2008;4(1):53-56.
10. Otmani S, Metzger D, Guichard N, et al. Effects of prolonged-release melatonin and zolpidem on postural stability in older adults. *Human Psychopharmacology* 2012;27(3):270-6.
11. Ministry of Health. Minutes of the 16th meeting of the Medicines Classification Committee held on the 24th of April 1996, 1996.
12. Buscemi N, Vandermeer B, Hooton N, et al. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. *Journal of General Internal Medicine* 2005;20(12):1151-8.
13. Buscemi N, Vandermeer B, Pandya R, et al. *Melatonin for Treatment of Sleep Disorders*. Rockville: Agency for Healthcare Research and Quality (US), 2004.
14. Sateia MJ. Update on sleep and psychiatric disorders. *Chest* 2009;135(5):1370-9.
15. Buscemi N, Vandermeer B, Friesen C, et al. Manifestations and management of chronic insomnia in adults. *Evidence Report/Technology Assessment No. 125 (Prepared by the University of Alberta Evidence-based Practice Center, under Contract No. C400000021.)*. Rockville: Agency for Healthcare Research and Quality, 2005.
16. Wilson JF. In the clinic. Insomnia. *Ann Intern Med* 2008;148(1):ITC13-1-ITC13-16.
17. Lemoine P, Wade AG, Katz A, et al. Efficacy and safety of prolonged-release melatonin for insomnia in middle-aged and elderly patients with hypertension: a combined analysis of controlled clinicl trials. *Integrated Blood Pressure Control* 2012;5:9-17.
18. Ramsawh HJ, Bloom HG, Ancoli-Israel S. Chapter 111 - Sleep, Aging, and Late-Life Insomnia. *Brocklehurst's Textbook of Geriatric Medicine and Gerontology*. 7th ed. Philadelphia: W.B. Saunders, 2010:943-48.
19. Silber MH, Krahn LE, Morgenthaler TI. *Sleep Medicine in Clinical Practice*. 2nd ed: Informa, 2010.
20. Otmani S, Metzger D, Guichard N, et al. Effects of prolonged-release melatonin and zolpidem on postural stability in older adults. *Hum Psychopharmacol* 2012.

21. Otmani S, Demazieres A, Staner C, et al. Effects of prolonged-release melatonin, zolpidem, and their combination on psychomotor functions, memory recall and driving skills in healthy middle aged and elderly volunteers. *Human Psychopharmacology* 2008.
22. Taylor DJ, Roane BM. Treatment of insomnia in adults and children: a practice-friendly review of research. *J Clin Psychol* 2010;66(11):1137-47.
23. Pharmaco. New Zealand Datasheet: Unisom SleepGels. Medsafe, 2008. http://www.medsafe.govt.nz/profs/Datasheet/u/Unisomsleepgels.pdf. [Last accessed: 23 January 2012.]
24. Basu R, Dodge H, Stoehr GP, et al. Sedative-hypnotic use of diphenhydramine in a rural, older adult, community-based cohort. Effects on cognition. *The American Journal of Geriatric Psychiatry* 2003;11(2):205-13.
25. Wang PS, Bohn RL, Glynn RJ, et al. Zolpidem use and hip fractures in older people. *J Am Geriatr Soc* 2001;49(12):1685-90.
26. Cumming RG, Le Couteur DG. Benzodiazepines and risk of hip fractures in older people: a review of the evidence. *CNS Drugs* 2003;17(11):825-37.
27. Wagner AK, Zhang F, Soumerai SB, et al. Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? *Archives of Internal Medicine* 2004;164(14):1567-72.
28. Zint K, Haefeli WE, Glynn RJ, et al. Impact of drug interactions, dosage, and duration of therapy on the risk of hip fracture associated with benzodiazepine use in older adults. *Pharmacoepidemiol Drug Saf* 2010;19(12):1248-55.
29. Glass J, Lanctot KL, Herrmann N, et al. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 2005;331(7526):1169.
30. Nowell PD, Mazumdar S, Buysse DJ, et al. Benzodiazepines and zolpidem for chronic insomnia. *Journal of the American Medical Association* 1997;278(24):2170-77.
31. Menkes DB, Shieffelbien LM, Huthwaite M. Hypnosedative access and risk of harm. *New Zealand Medical Journal* 2011;124(1345):69-73.
32. Charles J, Harrison CM, Britt H. Insomnia. *Australian Family Physician* 2009;38(5):283.
33. Glass J, Lanctot KL, Herrmann N, et al. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ* 2005;19;331:1169-76.
34. Kripke F.D. RDL, Lawrence E Kline. Hypnotics' association with mortality or cancer: a matched cohort study. *BMJ Open* 2012;2:e000850. doi:10.1136/bmjopen-2012-000850.
35. Jernelov S, Lekander M, Blom K, et al. Efficacy of a behavioral self-help treatment with or without therapist guidance for co-morbid and primary insomnia--a randomized controlled trial. *BMC Psychiatry* 2012;12:5.
36. Pharmacy Retailing (NZ) Ltd. New Zealand datasheet Normison. Medsafe, 2010. http://www.medsafe.govt.nz/profs/Datasheet/n/Normisontab.pdf. [Last accessed: 21 January 2012.]
37. Mylan New Zealand Limited. New Zealand datasheet Hypam. Medsafe, 2010. http://www.medsafe.govt.nz/profs/Datasheet/h/hypamtab.pdf. [Last accessed: 21 January 2012.]
38. Apotex NZ Ltd. New Zealand Data Sheet Apo-zopiclone. Medsafe, 2011. http://www.medsafe.govt.nz/profs/Datasheet/a/Apozopiclonetab.pdf. [Last accessed.]
39. Friborg O, Bjorvatn B, Amponsah B, et al. Associations between seasonal variations in day length (photoperiod), sleep timing, sleep quality and mood: a comparison between Ghana (5°) and Norway (69°). *Journal of Sleep Research* 2012;21(2):176-84.
40. Hirshkowitz M, Rose MW, Sharafkhaneh A. Chapter 6 - Neurotransmitters, Neurochemistry, and the Clinical Pharmacology of Sleep. In: Chokroverty S, editor. *Sleep Disorders Medicine (Third Edition)*. Philadelphia: W.B. Saunders, 2009:67-79.

41. Pharmacy Retailing (NZ) Ltd. New Zealand Datasheet: Circadin, 2011.
42. Mishima K, Okawa M, Shimuzu T. Diminished melatonin secretion in the elderly caused by insufficient environmental illumination. *J Clin Endocrinol Metab* 2001;86:129-34.
43. Cape G. Managing Insomnia. *Best Practice Journal* 2008(14):6-11.
44. Falloon K, Arroll B, Elley CR, et al. The assessment and management of insomnia in primary care. *BMJ* 2011;342:d2899.
45. Bent S, Padula A, Moore D, et al. Valerian for sleep: a systematic review and meta-analysis. *American Journal of Medicine* 2006;119(12):1005-12.
46. Baxter K, editor. *Stockley's Drug Interactions*. 8th ed. London: Pharmaceutical Press, 2008.
47. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2008.
48. Garfinkel D, Zorin M, Wainstein J, et al. Efficacy and safety of prolonged-release melatonin in insomnia patients with diabetes: a randomized, double-blind, crossover study. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* 2011;4:307-13.
49. Arendt J. Safety of Melatonin in Long-Term Use. *Journal of Biological Rhythms* 1997;12(6):673-81.
50. Palazidou E, Papadopoulos A, Ratcliff H, et al. Noradrenaline uptake inhibition increases melatonin secretion, a measure of noradrenergic neurotransmission, in depressed patients. *Psychological Medicine* 1992;22:309-15.
51. Skene DJ, Bojkowski CJ, Arendt J. Comparison of the effects of acute fluvoxamine and desipramine administration on melatonin and cortisol production in humans. *British Journal of Clinical Pharmacology* 1994;37(2):181-6.
52. Gauld N, Kelly F, Shaw J. Is non-prescription oseltamivir availability under strict criteria workable? A qualitative study in New Zealand. *J Antimicrob Chemother* 2011;66(1):201-04.
53. Gauld NJ, Jennings LC, Frampton C, et al. Five years of non-prescription oseltamivir: effects on resistance, immunisation and stock-piling [in press]. *J Antimicrob Chemother* 2012.