Submission for Reclassification of Melatonin

Executive Summary

This application is seeking the reclassification of melatonin in prolonged release 2mg oral dose form to Restricted Medicine (Pharmacist-Only Medicine). Melatonin 2mg prolonged release (CIRCADIN) was approved in NZ last year, as monotherapy for the short term 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 with increasing age, at a time when insomnia increases. Because melatonin has a short half-life, CIRCADIN is prolonged release to mimic the physiological release of melatonin.

Immediate release melatonin has been available for over 15 years, particularly in the US where it is a supplement, used by 5% of the population (2002). Melatonin is a Prescription Medicine in Australia, NZ (since 1996) and the UK, but was changed to supplement status in Canada in 2004.

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. With a low risk of side effects, lack of dependence and lack of abuse, this medicine has a favourable risk-benefit profile for non-prescription supply. Contraindications, precautions and interactions are all consistent with non-prescription availability.

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. Pharmacists will record supplies and the 13 week treatment period will be highlighted in pharmacist training and on product packaging. Patients needing melatonin beyond this point will receive doctor referral for a review of their insomnia. Sedating antihistamines are available for sleep as Pharmacist-Only Medicines, and also have a time-limit that pharmacists monitor. Pharmacists will be unable to supply melatonin outside of the licensed indication. This will be emphasised in training material and pharmacy organisations have agreed to highlight also. Pharmacists are used to ensuring appropriate supply of medicines, and used to turning down inappropriate requests, so this will be 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. It will include secondary causes of insomnia, referral points, lifestyle measures and duration of treatment.

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

Pharmacy Retailing (NZ) Ltd, trading as Healthcare Logistics

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

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

Alternative: Oral dose forms containing up to 2mg [assuming this entry would include prolonged release tablets]

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.[1] 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:

Preferred option (1): For oral use in prolonged release dose form containing 2mg or less.

Alternative option (2): in tablets or capsules containing 2mg or less. [We assume that this would allow prolonged release tablets of 2mg to be a restricted medicine.]

Quality efficacy data for the 2mg prolonged release tablet allows a risk-benefit analysis. A meta-analysis of melatonin in primary sleep disorders in 2005 (prior to publication of many of the CIRCADIN papers) 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.[2] As efficacy data for immediate release melatonin is insufficient, and therefore a risk-benefit assessment of the immediate release melatonin is not currently possible, we have presented two options. The first option 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 statements 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 with other sleep treatments.

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).[3] 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.[3]

In Canada, melatonin is approved as a medicinal ingredient or non-medicinal ingredient in natural health products,[email communication with Benjamin Mahon, Natural Health Products Directorate of Health Canada, 25 January 2012] changing from prescription only in 2004.[3]

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 is available in Appendix 1.

In the US where melatonin has always been considered a dietary supplement, 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 the UK commenced in June 2008. In Australia, following approval in December 2009, CIRCADIN was distributed from March 2010. CIRCADIN will be distributed in NZ from February 2012.

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 Consumer Medicine Information (CMI) 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 common in all ages, but particularly common in older people.[5] 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.[6] Insomnia increases risk of poor health (including psychiatric disorders),[7] reduces work performance and attendance, and quality of life,[5, 6] and predisposes sufferers to medical conditions such as hypertension.[5, 8] 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.[5] 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[9] or adverse cognitive effects.[10]

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,[11] and have been associated with cognitive impairment in elderly people.[12] Prescription hypnotics can cause dependence and tolerance, affect cognition and have been associated with falls.[6] 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 longer-term (up to 13 weeks) helps the insomniac to get back into a useful pattern of sleep rather than the recommended maximum of 7-10 consecutive days for sedating antihistamines,[11] and 2-4 weeks for benzodiazepines[13, 14] and zopiclone.[15]

Mode of action of melatonin

Melatonin is synthesised from serotonin and secreted by the pineal gland in a controlled fashion according to light/dark cycles.[16] 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.[17] Its primary effects are in the central nervous system where melatonin modulates synchronisation of the biological clock and promotes sleep. In blind-from-birth children, melatonin normalises their chaotic circadian sleep-wake rhythm.[16]

Melatonin has a very short half-life of 20-30 minutes in humans, which creates a difficulty for administering the medicine in an immediate release formulation.[16] However, the prolonged release CIRCADIN simulates the normal endogenous pharmacokinetic profile of melatonin. 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),[18] declining to baseline in 10 hours. The elderly have lower melatonin levels, and such depletion has been associated with insomnia.[19, 20] They also tend to have more transient arousals during sleep.[20] CIRCADIN is a

synthetically made melatonin, chemically identical to endogenous melatonin, which has been proven to improve sleep in the 55 year and older age group.[17] Response is higher in those with low nocturnal melatonin production.[19] Please see the datasheet (Appendix 3) for summaries of pivotal clinical trials demonstrating faster onset of sleep by 9-11 minutes, improved quality of sleep, morning alertness and quality of life, and reduced number of awakenings versus placebo. CIRCADIN availability without prescription, through the pharmacist as a Pharmacist-Only Medicine provides an effective 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. 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,[5, 6] 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 given) is assessing if secondary causes are likely 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.[3]

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[21] and Pharmacy Today, and a 2010 Sleep Medicine College of Pharmacists' update). History is the main diagnostic tool,[22] so appropriate questioning allows pharmacists to triage these patients, referring those where a secondary cause is likely. Additionally, lifestyle factors 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 secondary causes are likely (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 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. Unusually we have included information about prescription medicines because these are so commonly used, particularly in older people,[22] 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,[11] versus 13 weeks for CIRCADIN.[17] Sedating antihistamines have anticholinergic effects, causing adverse events including cognitive impairment, and have some contraindications, precautions, and interactions.[6, 11] 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”.[6]

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.[23] Other herbals have little evidence.[23]

Prescription hypnotics for sleep

While benzodiazepines and “z-drugs” are often used in general practice[22] (particularly in the elderly), there are drawbacks for some users. All hypnotics change sleep architecture, reducing slow wave sleep.[5] NZ datasheets for triazolam,[14] and temazepam[13] recommend short-term usage (2-4 weeks), and clinical efficacy for benzodiazepines tends to decline after 30 days of use.[6] Benzodiazepines can cause amnesia, confusion and impair co-ordination.[22] Likewise, zopiclone is not recommended for long-term use (longer than 4 weeks).[15] Withdrawal symptoms can occur with physical dependence, and there is a prolonged half-life in the elderly (7 hours).[15] These medicines are also subject to abuse and misuse, and interact with other CNS depressants including alcohol.

A meta-analysis of short-term treatment of people over 60 years old with sedative hypnotics (benzodiazepines and "z-drugs") found a small benefit.[24] 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), and the number needed to harm was 6. Adverse events were mostly reversible and not severe. Cognitive effects and morning or daytime fatigue were significantly more common with sedatives than placebo.

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.[10] For impaired memory, the effect from zolpidem remained significant the next morning.

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.[1] 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:[17]

- 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)[25], 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:[25]

- 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.[8]
- 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.[17]

Precautions[17]

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.[17]

> *"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.[26] 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.

Short-term melatonin is a relatively safe substance,[2, 3] 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.[17] 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.[17] No tolerance, rebound, or withdrawal effects were reported in an open study of 12 months treatment with CIRCADIN in 96 patients.[17] 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.[27] 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.[8]

The most recent periodic safety update report (PSUR) is 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) has received only four reports of adverse events (Appendix 6), all of which were graded as not serious and recovered without sequelae. The UK spontaneous reports (Drug Analysis Prints) received 85 ADR reports between 1963 and 17 November 2011 (first report 2001). Melatonin was 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 are 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_1324533282408.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.[3] 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.[3] This review noted that the safety over months and years remains unclear.[3] 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.[28]

US availability

Melatonin has been readily available on the US market since the mid-1990s. 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 melatonin

Looking more laterally, some drugs that increase 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).[29] 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.[30] 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.[31] 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.[17] Pharmacists will also be reminded about sleep hygiene and other matters 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. 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). Long-term usage will have occurred in the US where a large number of people report having taken the product, 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”, is not used recreationally, and does not cause dependence. Abuse is not a concern.

There is a potential for inappropriate 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 pharmacists are unable to supply oseltamivir in advance of need, and refused inappropriate requests,[31] 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 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.

As discussed above, the maximum 13-week period of use will be emphasised from Pharmacy Retailing (NZ), 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. A desire for continuation after 13 weeks will be referred to the doctor for review of insomnia therapy needs. When stopping the medication, there is no withdrawal and sleep variables gradually return to baseline.[18] Thus the consumer will be able to stop at the 13 week point.

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