Australian Government

Department of Health and Ageing

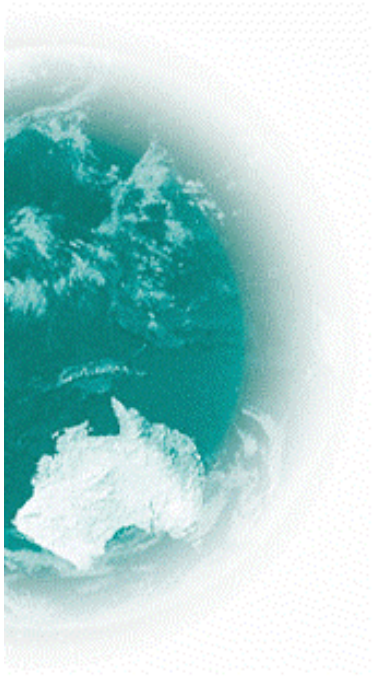
Therapeutic Goods Administration

# Australian Public Assessment Report for Melatonin

**Proprietary Product Name: Circadin**

**Submission No: PM-2010-01756-3-1**

**Sponsor: RAD Data Australia Pty Ltd**



***January 2011***

# Contents

# I. Introduction to Product Submission

## Submission Details

| | |
|---|---|
| *Type of Submission* | Extension of Indications |
| *Decision:* | Approved |
| *Date of Decision:* | 4 January 2011 |
| | |
| *Active ingredient(s):* | Melatonin |
| *Product Name(s):* | Circadin |
| *Sponsor's Name and Address:* | RAD Data Australia Pty Ltd<br>Level 7 Suite 2 of 100 Walker Street<br>North Sydney NSW 2060 |
| *Dose form(s):* | Modified release tablet |
| *Strength(s):* | 2 mg |
| *Container(s):* | Blister pack |
| *Pack size(s):* | 7 or 21 tablets |
| *Approved Therapeutic use:* | Monotherapy for the short term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over. |
| *Route(s) of administration:* | Oral |
| *Dosage:* | One tablet (2 mg) daily |
| *ARTG Number:* | 153959 |

## Product Background

This AusPAR describes the evaluation of an extension of indications submitted by Commercial Eyes Pty Ltd as an agent to the sponsor (RAD Data Australia Pty Ltd) for Circadin.

Melatonin is a naturally occurring hormone produced by the pineal gland. It has been widely used internationally as a treatment for insomnia and to modify circadian rhythms and is available without prescription in some jurisdictions, including the USA. Circadin, containing melatonin was registered in December 2009 after advice provided by the Australian Drug Evaluation Committee (ADEC) in October 2009.[1] The ADEC noted at that time that the available data indicated melatonin use is associated with a modest benefit in improving quality of sleep when used as monotherapy. The ADEC considered the available data were not adequate to support use in combination with other hypnotic agents. Additionally treatment should be limited to a maximum duration of three weeks consistent with the evidence from the pivotal efficacy studies for that submission (Neurim VII, Neurim IX).

Insomnia in the absence of a clear cause or associated medical, psychiatric or substance-use disorder is termed "primary insomnia" and becomes increasingly common with increasing age. Melatonin secretion varies with age and declines during adulthood such that by age 70 years, nocturnal melatonin concentration may be less than a quarter of that seen in early adulthood.

[1] TGA. AusPAR for Melatonin, 18 December 2009 (http://www.tga.gov.au/pmeds/auspar/auspar-circadin.pdf).

Other approved treatments for insomnia in Australia include benzodiazepines, zolpidem, an imidazopyridine, zopiclone, a cyclopyrrolone derivative and zaleplon, a pyrazolopyrimidine. All these medications are indicated for short-term treatment only and may be associated with dependence if used long term.

The requested indication for Circadin is as follows:

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

This change amends the current indication to remove a statement that described short term treatment as *up to three weeks.* It is proposed to extend the recommended duration of treatment to up to 13 weeks.

No change to the recommended daily dose of 2 mg once daily, one to two hours before bedtime and after food has been proposed.

### Regulatory Status

The product received initial ARTG Registration in December 2009.

The proposed extension of duration of use was approved by the European Medicines Agency (EMA) in April 2010. The indications in the European Union (EU) are as are proposed for Australia.

### Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

## *II. Quality Findings*

### Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

## *III. Nonclinical Findings*

### Nonclinical Summary and Conclusions

There was no requirement for a nonclinical evaluation in a submission of this type.

## *IV. Clinical Findings*

### Introduction

Study Neurim 112006 was designed to examine the short-term (3 weeks) efficacy (in improving sleep latency) and safety of Circadin versus placebo in adult insomniac patients aged 18-80 years with melatonin deficiency.[2] The United States Food and Drug Administration (FDA) also required evaluation of safety at three months for a short term indication. The study was modified to provide evidence to the FDA on whether the efficacy of Circadin in improving sleep latency is related to a patient's endogenous melatonin or to a patient's age by also assessing efficacy in patients aged 65-80 years regardless of their melatonin levels.

When it became apparent that there were considerable numbers of the patients (562/711; 80% of the long term intent to treat [ITT] full analysis population) who were 55 years and older the protocol had a further amendment (adding another primary objective). The amendment was submitted to the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) in September 2008 for the subset of patients in the 55 years and older subpopulation to compare sleep latency (the primary efficacy variable) and other efficacy outcomes beyond three weeks treatment. Thus two

[2] defined as excretion of ≤ 8 mcg/night of urinary 6-sulphatoxymelatonin (6-SMT), that is, "low secretors".

study reports for Study Neerim 112006 have been submitted; one enabling comparison of efficacy between low melatonin secretors[2] and the 65-80 years age groups over 3 weeks and one comparing efficacy between patients age ≥ 55 years and placebo over 26 weeks which was modified to emphasise the efficacy up to 13 weeks; both study reports however relate to the same study (with a late added primary objective).

## Pharmacokinetics/Pharmacodynamics

No new pharmacokinetic/pharmacodynamic data were submitted.

## Efficacy

### Pivotal Efficacy Study 112006

This was the original trial designed to provide evidence to the FDA on whether the efficacy of Circadin in improving sleep latency is related to patient's endogenous melatonin or to patient's age. It was conducted between October 2006 and December 2008 by general practitioners (GPs) in central Scotland.[3]. Quality of sleep assessments (relating the study to the TGA approved Indication) were only secondary and exploratory endpoints.

The primary objective was to compare the change in baseline in subjective sleep latency (as recorded in the Sleep Diary) after 3 weeks of double blind treatment with Circadin 2 mg or placebo in "low excretors" in patients aged 18-80 years.[4]

Secondary objectives included comparing the change in baseline in subjective sleep latency (as recorded in the Sleep Diary) in all patients aged 65-80 years and the change from baseline in subjective sleep maintenance (that is, number of times being awakened during the night, as recorded in the Sleep Diary) in "low excretors" aged 18-80 years, after 3 weeks of double blind treatment with Circadin 2 mg or placebo

A second primary objective was added by a protocol change. The added primary objective was to compare the percentage of patients aged 55-80 years in the Circadin 2 mg and placebo-treated groups who show improvement in clinically meaningful measures of night-time sleep quality and daytime quality of life following treatment for up to six months.[5,6]

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[3] Edinburgh latitude is 55° 57', Bass Strait is 40°, Darwin 12° 28' - there may be differences in melatonin levels as these relate to day length – see AusPAR for melatonin (http://www.tga.gov.au/pmeds/auspar/auspar-circadin.pdf).

[4] Sleep latency was assessed by:

- Sleep Diary (minutes) from the third question in the diary "Last night I fell asleep in":
- PSQI (see below) Component 2 is the sum of Question 2 score plus Question 5a which is: "During the past two weeks, how often have you had trouble sleeping because you cannot get to sleep within 30 minutes." On a 4 point rating from (0) Not during the past two weeks to (3) Three or more times a week.
- PSQI question 2 "How long (in minutes) has it taken you to fall asleep each night?" Score < 15 min (0), 16-30 min (1), 31-60 min (2), >60 min (3).
- Leeds Sleep Evaluation Questionnaire (LSEQ) getting to sleep was 3 VAS (100mm) responses to the question "How would you describe the way you currently fall asleep in comparison to usual?" - More difficult than usual, Easier than usual, Slower than usual, More quickly than usual, I feel less sleepy than usual, More sleepy than usual.

[5] Quality of sleep was assessed by:

1. Sleep Diary (quality) from the last question in the diary "I would rate my sleep quality last night": with a 4 point rating from Very good (0) to Very bad (3).
2. PSQI global (see below).
3. PSQI component 1 was the response to Question 9 "During the past two weeks, how would you rate your sleep Quality overall?" with a 4 point rating from Very good (0) to Very bad (3).
4. LSEQ – QOS was 2 VAS (100mm) responses to the question "How would you describe the quality of your. sleep compared to normal sleep?" More restless than usual, Calmer than usual, With more wakeful periods than usual, With less wakeful periods than usual.

[6] A responder was defined as a patient who becomes asymptomatic (that is, obtains a threshold mean score of 6 or less on the average global PSQI at Visits 6 and 7 relative to baseline).

Added long term secondary objectives were to compare in patients aged 55-80 years between the treatment groups sleep quality (mean global PSQI at Visits 6 [18 weeks of study extension] and 7[26 weeks of study extension]); quality of life (mean WHO-5 at Visits 6 and 7); subjective sleep latency (average score on question 2 of PSQI at Visits 6 and 7); withdrawal effect after discontinuation (Tyrer scale).[7,8,9]

Inclusion criteria were:

- Suffering from primary insomnia according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria (based on a sleep history questionnaire).
- Sleep latency of at least 20 minutes.
- Have not been using benzodiazepine (BZD) and non-BZD hypnotics for the past 2 weeks or more.
- Have not been using psychotropic treatments for the past 3 months or more.
- Stabilized on non-psychotropic treatments for more than 1 month.
- Completing the 2-week, placebo run-in period with correct use of the diary and LSEQ.

Exclusion criteria were:

- Use of BZDs or other hypnotics (including psychotropic treatments) during the study and preceding 2 weeks.
- Alcohol intake more than 30 g of pure alcohol per day and any intake after lunch-time.
- Pharmacological immunosuppression.
- Subjects belonging to the following groups were excluded: breathing related sleep disorder, circadian rhythm sleep disorder, dyssomnia, or sleep disorder due to general medical condition.
- Severe neurological, psychiatric disorders especially psychosis, anxiety, depression, dementia and alcoholism.
- Severe pain likely to interfere with sleep.
- Liver disease.
- Renal failure.
- Hypertension.
- Severe postural hypotension.

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[7] The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire which assesses sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score. Assessed over an 18-month period acceptable measures of internal homogeneity, consistency (test-retest reliability), and validity were obtained. A global PSQI score greater than 5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% (kappa = 0.75, p less than 0.001) in distinguishing good and poor sleepers. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989; 28:193-213.

[8] World Health Organisation - 5 Well being Index comprises 5 questions:

- I have felt cheerful and in good spirits
- I have felt calm and relaxed
- I have felt active and vigorous
- I woke up feeling fresh and rested
- My daily life has been filled with things that interest me

With each rated on a 6 point scale from All of the time to At no time.

[9] Tyrer questionnaire seeks the frequency (No, sometimes, often ) of 20 listed symptoms (and any other new symptoms).

- Congestive heart failure or recent myocardial infarction (within one year).
- Patients with an irregular lifestyle or life pattern (for example shift workers and patients likely to be jet lagged).

***Design, duration and type of study***

It was a randomised, double blind, placebo controlled parallel group study with:

- An initial 2-week run-in with single blind placebo.
- A 3-week treatment period 1:1 randomisation to double blind Circadin 2 mg or placebo.
- An offered 26-week extension period. Of those entering the extension all taking Circadin stayed on it and those on placebo were randomised on 1:1 to Circadin 2 mg or placebo.
- A 2 week run-out period – all received single blind placebo.

There were ten amendments considered substantial but of these the most relevant were:

- Amendment 1 (Sept 06) added some assessments including CGI scale.[10]
- Amendment 2 (Oct 06) added Sleep Diary assessments for long term visits and endocrine assessments.
- Amendment 3 (Feb 07) increased upper limit body mass index (BMI) to 40.
- Amendment 5 (Sept 07) combined the EU and US protocols to one protocol. .
- Amendment 10 (Sept 08 – that is, within 3 months of the last patient completing) added some objectives to assess efficacy and safety beyond 3 weeks.

***Comparator groups and endpoints***

The primary measure of efficacy was the change in baseline in sleep latency as recorded in the Sleep Diary after 3 weeks of double blind treatment in "low excretors" aged 18-80 years.

The added primary measure of efficacy was the number and percentage of patients aged 55-80 years at Visits 6 and 7 with a mean PSQI global score of ≤ 6 and an improvement from baseline of ≥ 10% in the mean WHO-5 index.

The secondary endpoints were the change in baseline in sleep latency as recorded in the Sleep Diary in all patients aged 65-80 years, and the change from baseline in sleep maintenance as recorded in the Sleep Diary in "low excretors" aged 18-80 years after 3 weeks of double blind treatment.

Exploratory outcomes (short term) included change from baseline in additional Sleep Diary variables, Pittsburgh Sleep Quality Index (PSQI) global score, Q2 and Q4 and individual components, WHO-5 Well-Being score, Clinical Global Impression Scale (CGIS) and the Leeds Sleep Evaluation Questionnaire (LSEQ) variable, after 3 weeks of double blind treatment.

Exploratory outcomes (long term) included change from baseline to up to 6 months of treatment in the efficacy variables of the Sleep Diary, PSQI, CGIS, and WHO5.

***Patient Disposition and Sample size***

Based on the estimated effect sizes and residual standard deviations (SDs) from those seen in previous studies, the sample size was derived to achieve 95% power at the 5% level for the primary objective using a 2-sample t-test and assuming a treatment effect of 19 minutes and an SD of 40.6 minutes. Thus 120 patients were required per group (480 total). However for 90% power at 5% the first secondary objective required 179 patients ≥ 65 years in the two groups thus an additional 150 patients in this age group were needed. To allow for attrition these figures were increased to 540 (in

[10] CGI = Clinical Global Impression Scale.

the each of the four groups, that is, high and "low excretors" taking placebo or Circadin) with 400 of these to be ≥ 65 years.

For the added primary variable based on a 2-sided 2-sample chi-square test estimated that 360 Circadin patients and 120 placebo patients would be needed to detect a difference at a 5% significance level with 85% power assuming the true response rates were 30% Circadin and 16% placebo. With 930 patients recruited this corresponded to 80% being in the 55-80 years age group and 65% providing data at Visits 6 and/or 7.

The numbers of patients in the "low excretors" (86 per treatment group) and 65-80 years year-old subgroups (Circadin 137; placebo 144) of the ITT population were less than planned. The study failed to meet the design requirements for statistical power of the primary (120 "low excretors" patients per treatment group) and secondary variables (179 patients ≥ 65 years per treatment group) involving sleep latency. The power reached with these sample sizes was 86% for the primary analysis and 82% for the first secondary analysis.

Patient disposition is summarised in Figures 1 and 2.

Figure 1: Overall patient disposition Study 112006.

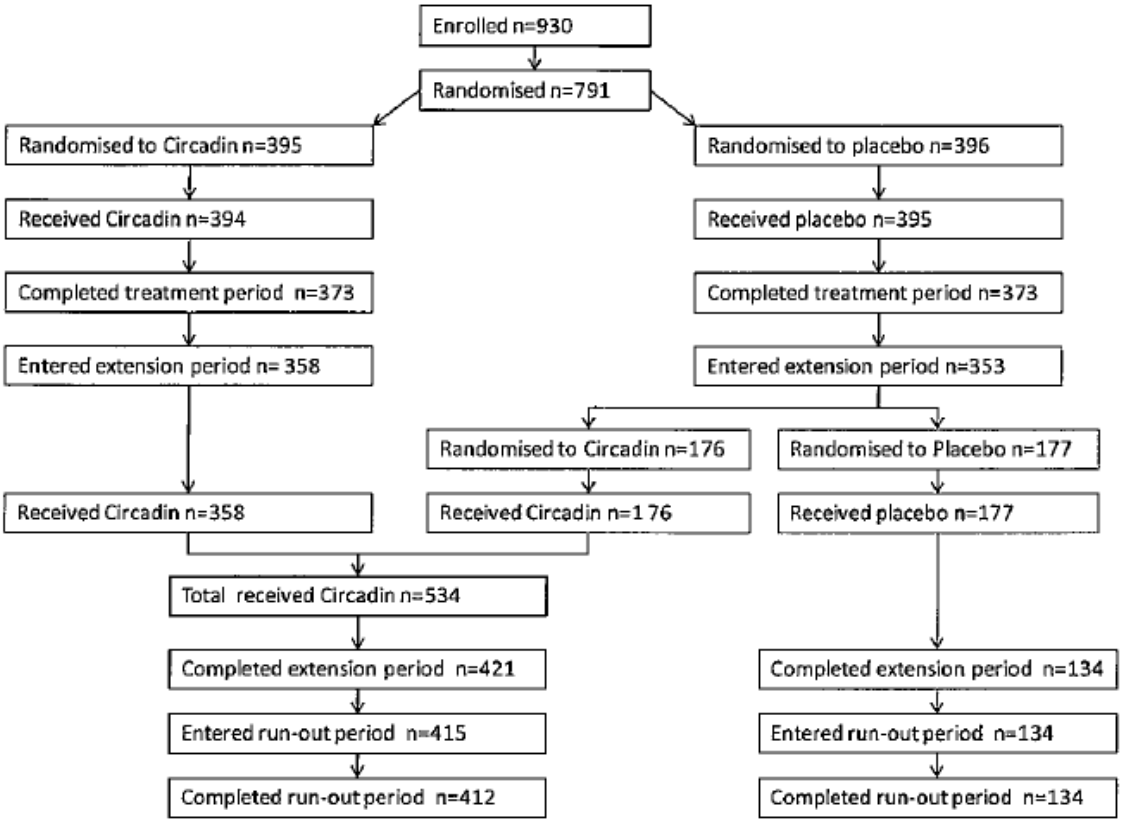
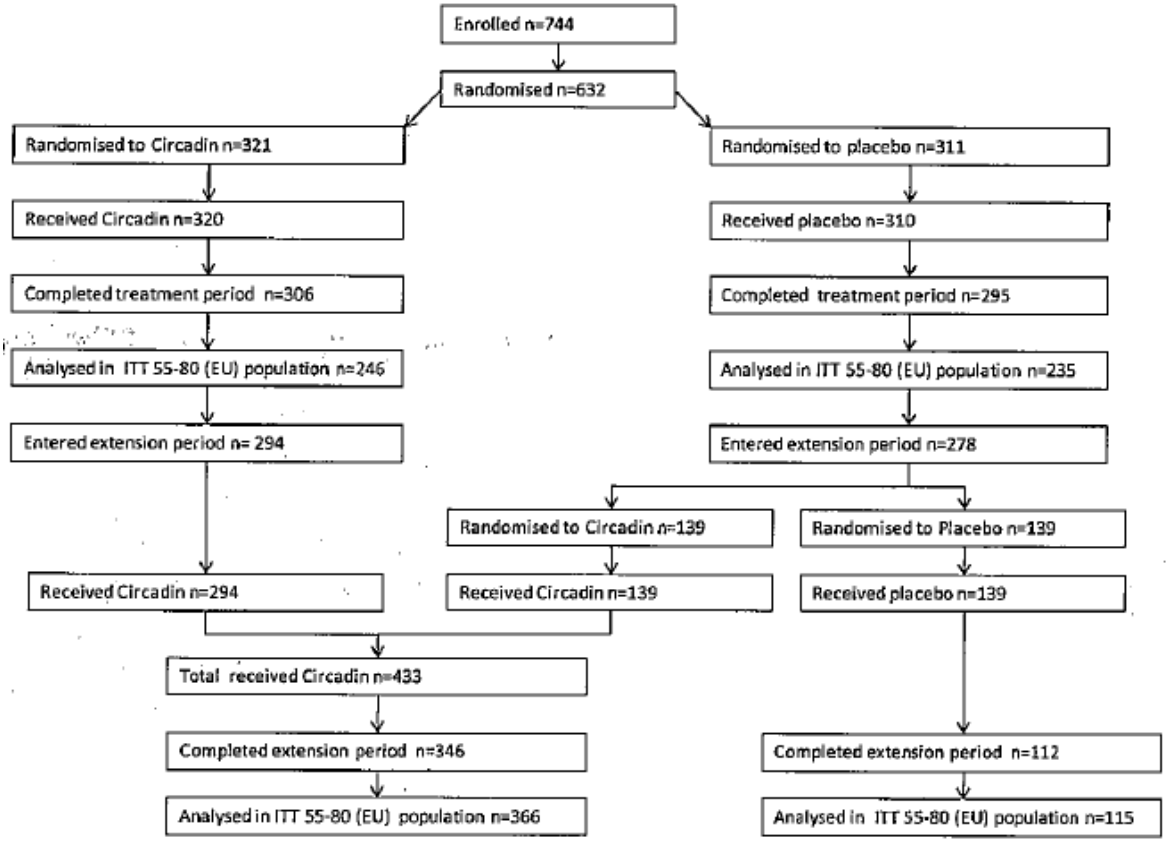


Figure 2: Patient disposition 55-80 years age group Study 112006.




### *Statistical methods*

*Primary analyses*

An analysis of covariance (ANCOVA) model was used to test the primary null hypothesis that the mean scores in change in sleep latency at 3 weeks were equal. The dependent variable was the mean score in sleep latency at Week 3; independent variables were the mean baseline sleep latency score and an indicator variable for treatment allocation and age category. The treatment effect estimate was to be reported, with a 95% Confidence Interval (CI) and p-value.

For the added primary hypotheses a $\chi^2$-test for association was used, with continuity correction, to test the null hypothesis that the percentages of patients that have a mean score of 6 or less on the global PSQI at Visits 6 and 7 are equal [11] (mean) and there is a 10% improvement at Visits 6 and 7 (mean) from baseline on the mean WHO-5 score; with the test statistic and corresponding p-value.

A log regression model with adjustment for randomisation stratification variables was then applied with the primary outcome as the response variable and an indicator variable for being in the Circadin group. The treatment effect estimate was to be reported as the odds ratio for achieving the primary outcome between the Circadin and placebo groups, with a 95% Cl.

[11] Weeks 23 and 31 when some patients had received 21 and 29 weeks Circadin and all had received at least 18 and 26 weeks of Circadin.

*Secondary analyses*

A similar ANCOVA analysis (to that for the primary variable) of the mean change at 3 weeks in sleep latency in patients of age 65-80 years and in sleep maintenance in the age 18-80 years "low excretors" was made.

For the added secondary variables there was also a similar ANCOVA analysis (to that for the added primary variable) of the mean change at Visits 6 and 7 in the PSQI global scores in the population aged 55-80 years; WHO-5 scores in the population aged 55-80 years and scores on Question 2 of the PSQI in the population aged 55-80 years.

*Exploratory Analyses*

For each of the short-term exploratory parameters (Sleep Diary variables, PSQI global score, Q2 and Q4 and individual components, WHO 5 and CGIS), the mean change at 3 weeks underwent similar ANCOVA for the "low excretors" population and various age bands, together with comparison between “low excretors” and high excretors.

Long term the development of any treatment effect differences over time was to be explored using appropriate ANCOVA models for the "low excretors" population and the ITT full analysis population in different age bands.

***Primary efficacy results***

For subjects aged 55 – 80 years, baseline PSQI (global) scores and WHO-5 scores were comparable between groups. Mean sleep latency at baseline for these subjects was 71.6 minutes in the Circadin group and 75.6 minutes in the placebo group.

*Primary variable*

In “low excretors” aged 18-80 years, the difference in sleep latency as measured by the Sleep Diary after 3 weeks of treatment between the Circadin and placebo groups was not significant (estimated difference -0.6 minutes, 95% CI -14.0 to 12.7, p=0.924).

*Added Primary variable*

The proportion of 55 to 80 year-old patients achieving a response after up to 6 months of treatment was higher in the Circadin than placebo groups but not significantly so, except at Visits 3, 5 and global treatment effect over the 6 months period (Table 1).[12]

Table 1: Primary response over time, summaries and mixed model results PSQI ≤ 6 and WHO-5 ≥ 110% of baseline Population EU ITT, 55-80 years

| | Treatment | | Treatment Effect Difference (Circadin-Placebo) |
|---|---|---|---|
| | Placebo | Circadin | |
| Visit | N/Total (%) | N/Total (%) | OR (95% CI), p-value |
| Visit 3 | 25/235 (10.6%) | 41/246 (16.7%) | 1.63 (1.01, 2.62), p=0.044 |
| Visit 4 | 23/115 (20.0%) | 86/365 (23.6%) | 1.34 (0.81, 2.21), p=0.258 |
| Visit 5 | 18/115 (15.7%) | 94/365 (25.8%) | 2.09 (1.23, 3.55), p=0.006 |
| Visit 6 | 33/115 (28.7%) | 101/365 (27.7%) | 1.01 (0.64, 1.59), p=0.966 |
| Visit 7 | 30/109 (27.5%) | 103/342 (30.1%) | 1.24 (0.79, 1.95), p=0.358 |
| | | Global Treatment Effect | 1.40 (1.02, 1.93), p=0.040 |

[12] Treatment response was defined as mean PSQI ≤ 6 and mean WHO-5 ≥ 110% of baseline at Visit 6 and Visit 7.

***Secondary and post-hoc efficacy outcomes***

*Secondary variables*

In the ITT 65-80 years population, the difference in sleep latency after 3 weeks of treatment between the Circadin and placebo groups was significant (-15.6 minutes; 95% CI -25.3 to -6.0, p = 0.002) (Table 2).

Table 2: Sleep latency at 3 weeks ITT 65-80 years Study 112006.

| Sleep latency Parameter | Treatment Change from Baseline Mean ± SD | | Difference (95%CIs) | p-value |
|---|---|---|---|---|
| | Circadin | Placebo | | |
| Sleep Diary (minutes) | -19.1 ± 47.3 | -1.7 ± 47.8 | -15.6(-25.3, -6.0) | 0.002 |
| PSQI Component 2 | -0.43 ± 0.87 | -0.22 ± 0.74 | -0.23 (-0.41, -0.04) | 0.018 |
| PSQI question 2 | -25.4 ± 50.9 | -8.9 ± 48.0 | -13.7 (-23.5, -3.9) | 0.006 |
| LSEQ getting to sleep | -3.4 ± 9.6 | -1.0 ± 8.0 | -2.0 (-3.9, 0.0) | 0.050 |

*Added Secondary variables*

Sleep quality with Circadin was not statistically significantly different compared with placebo after up to 6 months of treatment in the ITT 55-80 years population in most parameters at Weeks 6 and 7 (see Table 4). In the ITT 55-80 years population, there was varying difference in quality of life[13] score between the Circadin and placebo groups although it was significantly in favour of Circadin at Visit 7 (Table 3).

Table 3: Quality of Life WHO-5 aged 55-80 years.

| Parameter | | Treatment Effect Mean (SD) [N] | | Treatment Effect Difference (95%CIs) | p-value |
|---|---|---|---|---|---|
| | | Circadin | Placebo | | |
| WHO-5 | Visit 3 | 17.23(4.15) [246] | 17.26 (3.79) [235] | 0.27 (-0.25, 0.79) | P = 0.312 |
| | Visit 4 | 17.77 (3.95) [365] | 17.54 (4.08) [115] | 0.27 (-0.35, 0.89) | P = 0.391 |
| | Visit 5 | 17.91 (3.86) [366] | 17.49 (4.01) [115] | 0.47 (-0.19, 1.13) | P = 0.164 |
| | Visit 6 | 18.11 (3.72) [365] | 17.86 (4.28) [115] | 0.29 (-0.38, 0.95) | P = 0.400 |
| | Visit 7 | 18.07 (3.95) [346] | 17.61 (3.96) [112] | 0.71 (0.03, 1.39) | **P = 0.041** |

Sleep latency in the ITT 55-80 years population at Visit 6 and Visit 7, as assessed by some but not all parameters, was significantly shorter in the Circadin treatment group compared with placebo.

There was no evidence of an adverse withdrawal effect after 6 months of treatment with Circadin, with similar proportions of patients in both groups reporting new symptoms on the Tyrer questionnaire after the 2-week, placebo run-out period.

*Exploratory variables*

Of the 230 exploratory analyses of the 3-week data submitted only 37 showed a statistically significant result.

[13] as measured by the mean WHO-5 Index.

Sleep quality at 3 weeks was only improved in some parameters and groups, for example full ITT global PSQI, but not Sleep Diary.

Of the 114 exploratory analyses of the 26-week ITT data submitted only 27 showed a statistically significant result.

The evaluator noted that while there was no evidence of efficacy of Circadin in "low excretors" at 3 weeks (primary variable), in the secondary and exploratory variables for sleep latency at 3 weeks the 65-80 years age group taking Circadin were statistically superior to placebo although the CIs were wide.

***Quality of sleep***

This is the basis of the approved Indication. A similar picture to that for latency emerged with some but not all parameters showing significance at Visit 5 (Week 10 of extension) (Table 4). Excluding those taking placebo for 3 weeks and then Circadin for 26 weeks gave similar results, as were the results at the end of the 3-week study.

Table 4: Sleep quality ITT age 55-80 years ITT full analysis long term.

| Sleep quality Parameter | | Treatment Effect Mean (SD) [N] | | Treatment Effect Difference (95%CIs) | p-value |
|---|---|---|---|---|---|
| | | Circadin | Placebo | | |
| Sleep Diary (quality) | Visit 3 | 2.96 (0.80) [293] | 2.96 (0.73) [283] | 0.01 (-0.08, 0.10) | P = 0.869 |
| | Visit 4 | 2.85 (0.76) [405] | 2.87 (0.69) [131] | -0.05 (-0.16, 0.06) | P = 0.392 |
| | **Visit 5** | 2.73 (0.75) [375] | 2.78 (0.64) [113] | -0.07 (-0.19, 0.05) | P = 0.246 |
| | Visit 6 | 2.68 (0.78) [349] | 2.78 (0.71) [113] | -0.08 (-0.20, 0.05) | P = 0.230 |
| | Visit 7 | 2.68 (0.80) [333] | 2.76 (0.72) [108] | -0.08 (-0.20, 0.05) | P = 0.216 |
| PSQI global | Visit 3 | 8.52 (3.49) [293] | 8.82 (3.27) [284] | -0.53 (-0.97, -0.10) | P = **0.015** |
| | Visit 4 | 7.61 (3.58) [414] | 8.03 (3.30) [133] | -0.44 (-0.96, 0.09) | P = 0.102 |
| | **Visit 5** | 7.20 (3.49) [385] | 7.84 (3.50) [124] | -0.67 (-1.22, -0.12) | **P = 0.017** |
| | Visit 6 | 6.94 (3.49) [365] | 7.58 (3.62) [115] | -0.63 (-1.21, -0.06) | P = **0.031** |
| | Visit 7 | 6.78 (3.59) [341] | 7.23 (3.62) [109] | -0.38 (-0.96, 0.20) | P = 0.196 |
| PSQI component 1 | Visit 3 | 1.47 (0.77) [293] | 1.51 (0.75) [284] | -0.08 (-0.19, 0.03) | P = 0.149 |
| | Visit 4 | 1.27 (0.74) [414] | 1.29 (0.77) [133] | -0.08 (-0.21, 0.05) | P = 0.237 |
| | **Visit 5** | 1.21 (0.74) [385] | 1.31 (0.74) [124] | -0.16 (-0.30, -0.03) | **P = 0.018** |
| | Visit 6 | 1.15 (0.77) [365] | 1.21 (0.87) [115] | -0.11 (-0.25, 0.04)_ | P = 0.142 |
| | Visit 7 | 1.14 (0.75) [341] | 1.17 (0.84) [109] | -0.08 (-0.22, 0.07) | P = 0.300 |

***Sleep Latency***

Sleep latency is shown in at Visit 6 and Visit 7 in those aged 65-80 years in Table 5 and at 3 weeks in those aged 55-80 years in Table 6. However after 4 weeks of the study extension (Visit 4) the effects for latency were not statistically significant in the 55-80 years age group (Table 7).

Visit 5 was Week 15 (Day 105 of the study). This corresponds to 2 weeks of placebo and 3 weeks of treatment (Circadin or placebo). The initial Circadin patients then received another 10 weeks of Circadin (total 13 weeks of Circadin; 2 weeks placebo), while some of the initial placebo patients received Circadin (total 10 weeks of Circadin plus 5 weeks placebo) and other initial placebo

patients stayed on placebo (total 15 weeks placebo). This is the source of the 3-month data (Table 8).

Table 5: Sleep latency at Visit 6 and 7 (18 and 26 weeks of study extension) ITT 65-80 years Study 112006

| Sleep latency Parameter | | Treatment Effect Mean ± SD | | Treatment Effect Difference (95%CIs) | p-value |
|---|---|---|---|---|---|
| | | Circadin | Placebo | | |
| Sleep Diary(minutes) | Visit 6 | 48.4 ± 41.5 | 74.1 ± 65.8 | -18.8(-29.5, -8.1) | 0.001 |
| | Visit 7 | 49.1 ± 42.9 | 72.8 ± 65.9 | -15.3 (-26.4, -4.1) | 0.007 |
| PSQI Component 2 | Visit 6 | 1.81 ± 1.09 | 2.22 ± 1.12 | -0.31 -0.55, -0.08) | 0.009 |
| | Visit 7 | 1.76 ± 1.10 | 2.13 ± 1.12 | -0.21 (-0.44, 0.03) | 0.082 |
| PSQI question 2 | Visit 6 | 44.3 ± 41.8 | 71.6 ± 78.1 | -20.2 (-31.9, -8.5) | 0.001 |
| | Visit 7 | 44.3 ± 43.5 | 65.6 ± 61.3 | -11.2 (-23.0, 0.7) | 0.064 |

Table 6: Sleep latency at 3 weeks ITT aged 55-80 years.

| Sleep latency Parameter | Treatment Change from Baseline Mean ± SD | | Difference (95%CIs) | p-value |
|---|---|---|---|---|
| | Circadin | Placebo | | |
| Sleep Diary (minutes) | -15.4 ± 44.4 | -5.5 ± 43.2 | -7.8 (-14.1, -1.6) | 0.014 |
| PSQI Component 2 | -0.41 ± 0.78 | -0.22 ± 0.72 | -0.18 (-0.3, -0.05) | 0.005 |
| PSQI question 2 | -22.0 ± 47.2 | -9.7 ± 42.6 | -9.4(-15.7, -3.1) | 0.003 |
| LSEQ getting to sleep | -4.2 ± 10.1 | -2.0 ± 9.9 | -2.1(-3.7, -0.6) | 0.006 |

Table 7: Sleep latency at Visit 4 (4 weeks of study extension Circadin) ITT aged 55-80years.

| Sleep latency Parameter | Treatment Effect Mean ± SD | | Treatment Effect Difference (95%CIs) | p-value |
|---|---|---|---|---|
| | Circadin | Placebo | | |
| Sleep Diary (minutes) | 53.5 ±47.9]404] | 62.9 ± 51.7[132] | -5.8(-12.4, 0.9) | 0.088 |
| PSQI Component 2 | 1.95 ± 1.08[414] | 2.05 ± 1.09[133] | -0.08(-0.24, 0.08) | 0.326 |
| PSQI question 2 | 47.8 ± 48.3[414] | 59.9 ± 60.3[133] | -5.2(-12.1, 1.8) | 0.147 |

Table 8: Sleep latency at Visit 5 (10 weeks of study extension Circadin) ITT aged 55-80years.

| Sleep latency Parameter | Treatment Effect Mean ± SD[N] | | Treatment Effect Difference (95%CIs) | p-value |
|---|---|---|---|---|
| | Circadin | Placebo | | |
| Sleep Diary (minutes) | 50.0 ± 46.3[376] | 63.0 ± 52.3[114] | -9.7(-16.0, -2.6) | 0.007 |
| PSQI Component 2 | 1.83 ± 1.14[385] | 2.05 ± 1.12[124] | -0.17(-0.33, 0.00) | 0.052 |
| PSQI question 2 | 43.5 ± 44.3[385] | 57.7 ± 57.5[124] | -7.8 (-15.2, -0.4) | 0.040 |

Patient response is shown in Table 9.

Table 9: Treatment Response,* patient nos. (%) / time, MMRM results, ITT 55-80 years (EU) population.

| Visit | Circadin | Placebo | Treatment Effect difference Circadin – placebo | |
|---|---|---|---|---|
| | N/Total (%) | N/Total (%) | Odds ratio (95% CI) | p-value |
| Visit 3 | 41/246 (16.7%) | 25/235 (10.6%) | 1.63 (1.01, 2.62) | p=0.044 |
| Visit 4 | 86/365 (23.6%) | 23/115 (20.0%) | 1.34 (0.81, 2.21) | p=0.258 |
| Visit 5 | 94/365 (25.8%) | 18/115 (15.7%) | 2.09 (1.23, 3.55) | p=0.006 |
| Visit 6 | 101/365 (27.7%) | 33/115 (28.7%) | 1.01 (0.64, 1.59) | p=0.966 |
| Visit 7 | 103/342 (30.1%) | 30/109 (27.5%) | 1.24 (0.79, 1.95) | p=0.358 |
| | Global Treatment Effect | | 1.40 (1.02, 1.93) | p=0.040 |

## Other Safety Studies

### *Study 12545A*

Study 12545A was a post marketing surveillance study conducted in Germany by Lundbeck GmbH with GPs, neurologists, psychiatrists paid per patient for participating.

The objective was to investigate the safety and effectiveness of a 3-week treatment with Circadin 2 mg in patients aged 55 years and above with primary insomnia. The aim of this study was to investigate discontinuation, withdrawal and rebound effects of Circadin 2 mg in the general population under normal prescribing conditions according to the EU SmPC (Summary of Product Characteristics). The study objectives were:

- Analysis of rebound insomnia defined as worse sleep quality or morning alertness after stopping Circadin treatment, as compared to before initiating Circadin treatment.
- Analysis of withdrawal symptoms evaluated by comparing the incidence of adverse events during Circadin treatment compared to the incidence after stopping Circadin treatment.

Any patient who initiated Circadin treatment could be included in the study if this fell within current practice according to the SmPC. For the selection of patients, the indication and contraindications of Circadin 2 mg had to be considered. Circadin was to be prescribed by the physician according to the therapeutic needs of each patient, in accordance with the SmPC.

A total of 625 patients were planned to be included in the study with an estimated drop-out rate of 20 % to include at least 500 patients with evaluable withdrawal data.

The main endpoints were sleep quality assessed in the categories very good, good, fair, bad and very bad as well as morning alertness classified as very alert, alert, fair, tired and very tired and adverse events. They were assessed while taking Circadin, immediately after stopping Circadin (early withdrawal) and within weeks of treatment discontinuation (late withdrawal).

Statistical analyses were descriptive with 2-sided 95% CIs calculated for rebound effects on sleep quality and morning alertness.

The majority of patients (318, 53.3%) had moderate insomnia while 226 patients (37.9%) had severe insomnia. A total of 597 patients started the study with premature termination occurring in 133 patients. The major reason for termination was not specified (85, 14.2%) and small numbers terminated for patient's wish (18, 3.0%), lack of efficacy (14, 2.3%) and adverse events (13, 2.2%).

At least 11.4% took other sleeping pills during Circadin treatment.

*Primary efficacy results*

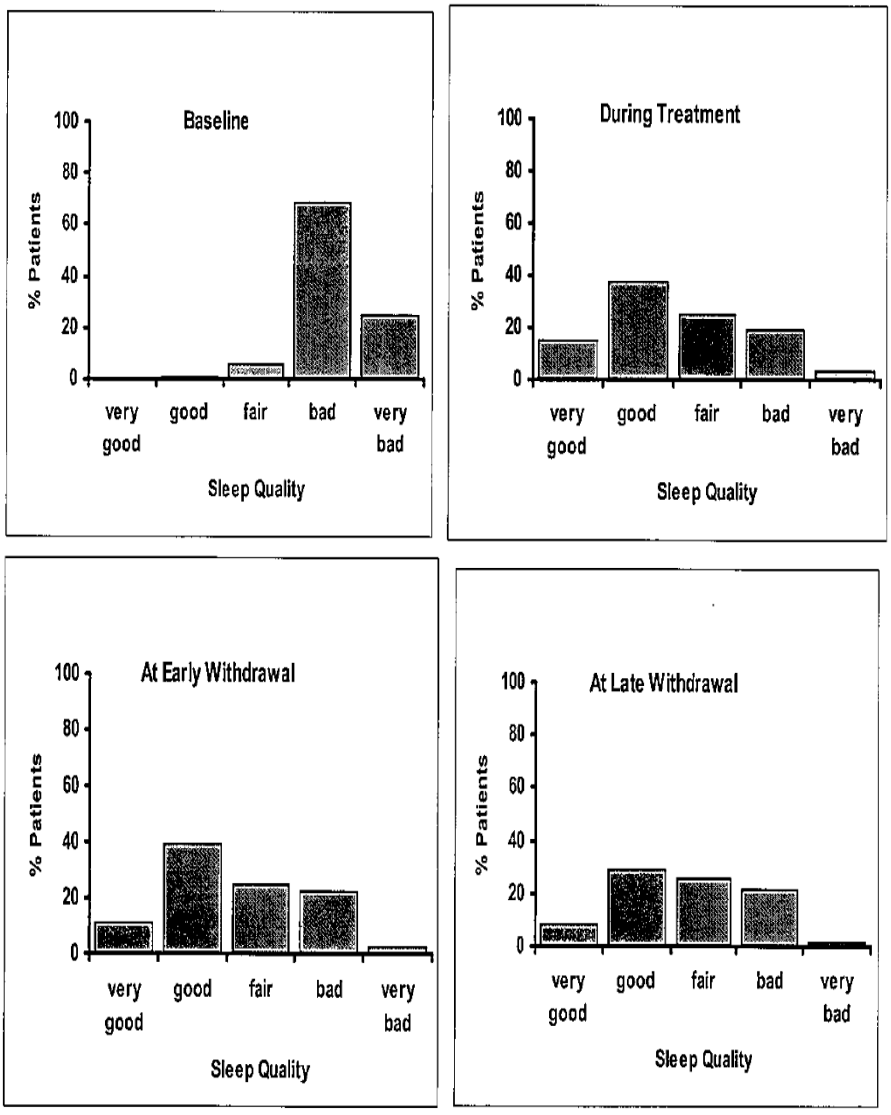
Improvement, or deterioration from baseline, was defined as a change of at least one point. The mean value improved from 4.2 ± 0.6 at baseline to 2.6 ± 1.1 during treatment, and was 2.7 ± 1.0 at early withdrawal and 2.8 ± 1.0 at late withdrawal.

Sleep quality was improved in 486 patients (81.4%) during treatment, and was still better in 478 patients (80.1%) at early withdrawal (within days) and in 396 patients (66.3%) at late withdrawal (within weeks) compared to baseline (Figure 3).

Deterioration (rebound insomnia analysis) was observed for 19 patients (3.2%) during treatment at early withdrawal, and for 12 patients (2.0%) at late withdrawal. Fourteen of the 19 patients (73.7%) that deteriorated at early withdrawal and 9 of the 12 patients (75.0%) that deteriorated at late withdrawal also deteriorated during treatment. Thus it could be assumed that deterioration was not due to rebound.

It was planned to compare withdrawal symptoms (AEs) between early and late withdrawal, however AEs were reported during treatment but none after withdrawal of treatment.

Figure 3: Sleep quality[a] at baseline, during treatment, and at early and late withdrawal (N=597)




[a] Severity was classified as 1=very good, 2=good, 3=fair, 4=bad and 5=very bad

### Summary of Efficacy

The pivotal study NEU 11206 was essentially a 3-week efficacy study with a safety extension out to 3 months. It was modified 9 months after commencement to enable a comparison of age groups with "low excretors". Just before completion, apparently after all subjects were enrolled, it was again modified to enable presentation of 3 months efficacy comparison with placebo in those subjects aged 55-80 years.

The study failed to achieve statistical significance in either the primary variable or the added primary variable.

In the secondary variables for the ITT 65-80 years population, the difference in sleep latency after 3 weeks of treatment between the Circadin and placebo groups was significant. Since there was no difference for the "low excretors" it suggests an age effect rather than low levels was responsible for efficacy in the older age group. This statement needs to be qualified by the failure to achieve significance for either of the primary variables.

Of the added secondary variables in the ITT 55-80 years population sleep latency at Visit 6 and Visit 7, as assessed by some but not all parameters, was significantly shorter in the Circadin treatment group, while sleep quality was improved in only one parameter and only at Visit 6.

Of the 114 exploratory analyses of the 26-week ITT data submitted only 27 showed a statistically significant result and of the 230 exploratory analyses of the 3-week data submitted only 37 showed a statistically significant result.

Of the exploratory analyses relevant to the application:

- At 13 weeks the Circadin group contained approximately one third that had taken the drug for 10 weeks and two thirds that had taken it for 13 weeks. The only time that this group achieved a significantly greater number of responders after Week 3 was Visit 5 (it failed to do so at Visit 4 [Week 9] and Visits 6 and 7 [the primary endpoints]).
- At Week 9 and Week 13 the only sleep quality parameters that showed significant difference from placebo were the PSQI global and PSQI component 1 at Week 13; neither these parameters nor the other parameter (the Sleep Diary – quality) showed significant difference from placebo at Week 9. The EMA report response 2 contained analyses without those switching from placebo to Circadin at 3 weeks. It only analysed PSQI global in relation to quality of sleep. It did not affect the above comments.
- At the end of the 3-week study in relation to quality of sleep, only PSQI global showed significant difference from placebo, there being no significant difference for PSQI component 1, Sleep Diary (quality) or LSEQ QOS.

In the sponsor's response to the EMA evaluation it was argued that efficacy parameters other than sleep latency should be considered.

- At Week 13 sleep latency parameters that showed significant difference from placebo were the Sleep Diary and PSQI question 2 (Table 8). Component 2 of the PSQI demonstrated evidence of benefit (p =0.052). These parameters at Week 9 did not show significant difference from placebo (Table 7).

The application is thus based on an isolated exploratory analysis in a study that failed to achieve its primary objectives and many of its secondary objectives.

## Safety

### Extent and Duration of Exposure

In the sponsor's *Summary of Clinical Safety* there were data on 3194 patients taking Circadin in all of the studies assessing efficacy. Of these, 1850 were in studies which had data on length of

exposure enabling AE incidence rates to be calculated (Table 10). A total of 794 patients were treated for 6 months and 146 for ≥ 1 year.

Table 10: Overall summary of patient weeks of exposure.

| | Average Total Patient Weeks of Exposure | |
|---|---|---|
| Protocol | Circadin | Placebo |
| 30424 + Neurim I + Neurim IV | 3156.47 | 380.16 |
| Neurim V | 1165.05 | 2471.03[a] |
| Neurim V Open | 9187.03 | 0 |
| Neurim VII | 276.60 | 273.70 |
| Neurim VIII | 765.80 | 849.90 |
| Neurim IX | 707.14 | 716.57 |
| Neu 112006 | 15341.14 | 5913.71 |
| Total | 30599.23 | 10605.07 |

[a] Includes single blind placebo exposure.

## Adverse Events (AEs)

### *All Studies*

AEs were low and comparable between Circadin and placebo (Table 11).

Table 11: Overall AEs with an incidence ≥ 1%.

| Preferred Term | Circadin N = 1931 | | Placebo N = 1642 | |
|---|---|---|---|---|
| | n | % | n | % |
| **Any event** | 942 | 48.8 | 621 | 37.8 |
| Abdominal pain | 21 | 1.1 | 11 | 0.7 |
| Abdominal pain upper | 20 | 1 | 20 | 1.2 |
| Constipation | 23 | 1.2 | 14 | 0.9 |
| Diarrhoea | 60 | 3.1 | 29 | 1.8 |
| Nausea | 34 | 1.8 | 27 | 1.7 |
| Vomiting | 28 | 1.5 | 14 | 0.9 |
| Asthenia | 37 | 1.9 | 19 | 1.2 |
| Influenza | 29 | 1.5 | 14 | 0.9 |
| Lower respiratory tract infection | 37 | 1.9 | 19 | 1.2 |
| Nasopharyngitis | 78 | 4.0 | 49 | 3.0 |
| Pharyngitis | 37 | 1.9 | 20 | 1.2 |
| Upper respiratory tract infection | 56 | 2.9 | 20 | 1.2 |
| Urinary tract infection | 40 | 2.1 | 12 | 0.7 |
| Arthralgia | 68 | 3.5 | 29 | 1.8 |
| Back pain | 74 | 3.8 | 24 | 1.5 |
| Muscle cramps | 21 | 1.1 | 10 | 0.6 |
| Neck pain | 21 | 1.1 | 10 | 0.6 |
| Pain in extremity | 31 | 1.6 | 18. | 1.1 |
| Dizziness | 31 | 1.6 | 19 | 1.2 |
| Headache | 110 | 5.7 | 102 | 6.2 |
| Migraine | 21 | 1.1 | 19 | 1.2 |
| Anxiety | 20 | 1.0 | 19 | 1.2 |
| Cough | 42 | 2.2 | 21 | 1.3 |
| Pharyngolaryngeal pain | 29 | 1.5 | 14 | 0.9 |
| Rhinitis | 21 | 1.1 | 15 | 0.9 |

### *Pivotal Study 112006*

The only significant difference between treatments was a higher incidence of drug-related AEs on placebo in the Extension period (Table 12). In the first 3 weeks, a drug-related AE occurred in 4.8% in the Circadin group (vs 5.1% placebo). In the 26-week extension period, a drug-related AE occurred in 13.1% (vs 15.3% placebo) and in the withdrawal phase, a drug-related AE occurred in 0.7% (vs 0.7% placebo). For those in the 55-80 years age groups there were 0.6% drug-related AEs in the Circadin group (vs 0 placebo) in the first 3 weeks, 0.5% (vs 1.45%) in the extension phase and none during withdrawal.

Table 12: Number (%) of patients who had an AE in treatment and extension periods, safety 55-80 years population, Study 112006.

| Category of AE | Treatment period | | Extension period | |
|---|---|---|---|---|
| | Circadin | Placebo | Circadin | Placebo |
| No of patients | 320 | 310 | 433 | 139 |
| Any AE | 109 (34.1 %) | 124 (40.0%) | 319 (73.7%) | 112 (80.6%) |
| Any SAE | 1 (0.3%) | 3 (1.0%) | 15 (3.5%) | 8 (5.8%) |
| SAE leading to death | 0 (0%) | 0 (0%) | 0 (0%) | 1 (0.7%) |
| DAE | 7 (2.2%) | 7 (2.3%) | 23 (5.3%) | 8 (5.8%) |
| Drug-related AE[a] | 17 (5.3%) | 19 (6.1%) | 56 (12.9%) | 24 (17.3%) |
| Drug-related SAE[a] | 0 (0%) | 0 (0%) | 1 (0.2%) | 0 (0%) |

[a] Assessed by the investigator as definitely, probably or possibly related to study drug
DAE Premature discontinuation of treatment due to an AE Percentages based on number of patients in the safety population for each treatment group

There was an increase in infections seen in the submitted data. However when adjusted for exposure the rates were similar.

There was one patient taking Circadin who reported five serious adverse events (SAEs) in the withdrawal phase but they were considered to be unrelated by the investigators. Laboratory results were comparable. In assessing endocrine levels they were generally similar but variation was wide and numbers were small in the relevant population. Synacthen tests were similar but again variation was wide and numbers were small in the relevant population (males ≥ 50 years, 13 patients vs 2).

Sleep quality rebound effects were similar between Circadin and placebo (Table 13)

Table 13: Sleep quality rebound effects as assessed by the Sleep Diary in the week after Visit 7, by Visit 3 randomisation for the safety 55-80 years population, Study 112006.

| Sleep quality (Sleep diary) | Circadin (n=433) | Placebo(n=138) |
|---|---|---|
| **Baseline** | | |
| N | 432 | 138 |
| Mean (SD) | 3.13 (0.69) | 3.13 (0.66) |
| Median | 3.14 | 3.14 |
| Min, Max | 1.00, 5.00 | 1.00, 5.00 |
| **Average Visit 7 + 1 week** | | |
| N | 145 | 53 |
| Mean (SD) | 2.63 (0.80) | 2.73 (0.68) |
| Median | 2.57 | 2.86 |
| Min, Max | 1.00, 5.00 | 1.00, 4.14 |
| **Difference: Visit 7 + 1 week - Baseline** | | |
| N | 145 | 53 |
| Mean (SD) | -0.49 (0.68) | -0.37 (0.78) |
| Median | -0.43 | -0.29 |
| Min, Max | -2.57, 1.29 | -3.14, 1.07 |

Sleep Diary Sleep Quality: 1 = V. Good to 5 = V. Bad

### *Other study 12545A*

In this post marketing study almost all AEs (75 out of 79) were considered related to Circadin (Table 14). The exceptions were gastric ulcer; and anxiety/depression/restlessness. There were no AEs of concern.

Table 14: Patients reporting AEs during Circadin 2 mg treatment Study 12545A.

| Patients with Adverse Events[a] | | Total (n=652) | |
|---|---|---|---|
| MedDRA System Organ Class[14] | MedDRA Preferred Term | N | % |
| Cardiac disorders | Palpitations | 1 | 0.2 |
| Ear and labyrinth disorders | Tinnitus | 1 | 0.2 |
| Eye disorders | Visual impairment | 1 | 0.2 |
| Gastrointestinal disorders | Abdominal distension | 1 | 0.2 |
| | Abdominal pain lower | 1 | 0.2 |
| | Abdominal pain upper | 1 | 0.2 |
| | Constipation | 3 | 0.5 |
| | Diarrhoea | 4 | 0.6 |
| | Dry mouth | 1 | 0.2 |
| | Nausea | 2 | 0.3 |
| | Vomiting | 10 | 1.5 |
| General disorders and administration site conditions | Irritability | 2 | 0.3 |
| Investigations | Blood glucose decreased | 1 | 0.2 |
| | Weight increased | 1 | 0.2 |
| Metabolism and nutrition disorders | Anorexia | 1 | 0.2 |
| Nervous system disorders | Coordination abnormal | 1 | 0.2 |
| | Dizziness | 1 | 0.2 |
| | Headache | 5 | 0.8 |
| | Hemicephalalgia | 5 | 0.8 |
| | Paraesthesia | 1 | 0.2 |
| | Poor quality sleep | 1 | 0.2 |
| | Restless legs syndrome | 1 | 0.2 |
| Psychiatric disorders | Anxiety | 1 | 0.2 |
| | Apathy | 1 | 0.2 |
| | Depressed mood | 1 | 0.2 |
| | Depression | 1 | 0.2 |
| | Hallucination | 1 | 0.2 |
| | Insomnia | 1 | 0.2 |
| | Middle insomnia | 3 | 0.5 |
| | Nervousness | 1 | 0.2 |
| | Nightmare | 3 | 0.5 |
| | Restlessness | 5 | 0.8 |

[14] MedDRA = Medical Dictionary for Regulatory Activities

| | | | |
|---|---|---|---|
| | Sleep disorder | 1 | 0.2 |
| | Sleep talking | 1 | 0.2 |
| Respiratory, thoracic and mediastinal disorders | Dyspnoea | 1 | 0.2 |
| Skin and subcutaneous tissue disorders | Eczema | 1 | 0.2 |
| | Erythema | 1 | 0.2 |
| | Hyperhidrosis | 3 | 0.5 |
| | Night sweats | 2 | 0.3 |
| | Pruritus generalised | 2 | 0.3 |
| Vascular disorders | Hotflush | 2 | 0.3 |
| | Venous insufficiency | 1 | 0.2 |

[a] Multiple answers possible.

### Deaths and Other Serious Adverse Events

There were no treatment-related deaths or SAEs. In the trials there were 4 deaths and 61 SAEs.

### Withdrawals due to adverse events

The sponsor's *Summary of Clinical Safety* states there were 72/2486 (2.9%) discontinuations due to AEs on Circadin and 62/1558 (4.0%) on placebo. However, using the submitted data from all studies including 112006 and 12545A the evaluator obtained 76 discontinuations due to AEs in the Circadin group of which 57 were possibly or probably related to the drug.

### Laboratory Data

No significant changes were found in short or long term studies.

### Effect on Vital Signs and ECG

No significant changes were found in short or long term studies.

### Safety Summary and Conclusions

No significant changes were found in short term (3 weeks) or long term studies (up to 18 months)

## Overall Conclusion and Risk/Benefit Assessment

The safety of Circadin shown in the long term study 112006, both during treatment and on withdrawal was generally comparable to placebo.

In relation to efficacy: The pivotal study NEU 11206 was a 3-week efficacy study with a safety extension out to 3 months that had two major modifications. The study failed to achieve statistical significance in either the primary variable or the added primary variable. Of the 114 exploratory analyses of the 26-week ITT data submitted only 27 showed a statistically significant result. Of the exploratory analyses relevant to the application:

- The only time that the Circadin group achieved a significantly greater number of responders after Week 3 was Visit 5 (it failed to do so at Visit 4 [week 9] and Visits 6 and 7 [the primary endpoints]).
- At Week 9 and Week 13 the only sleep quality parameters that showed significant difference from placebo were the PSQI global and PSQI component 1 at Week 13; neither these parameters nor the other parameter (the Sleep Diary – quality) showed significant difference from placebo at Week 9. The EMA report response 2 contained analyses without those switching from placebo to Circadin at 3 weeks. It only analysed PSQI global in relation to quality of sleep. It did not affect the above comments

- At the end of the 3-week study in relation to quality of sleep, only PSQI global showed significant difference from placebo, there being no significant difference for PSQI component 1, Sleep Diary (quality) or LSEQ QOS.

The application is thus based on an isolated exploratory analysis in a study that failed to achieve its primary objectives and many of its secondaries.

The evaluator did not recommend that the extension of Indications be approved.

## V. Pharmacovigilance Findings

There was no requirement for a Risk Management Plan evaluation in a submission of this type.

## VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

### Quality

There was no requirement for a quality evaluation in a submission of this type.

### Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

### Clinical

#### Efficacy

One efficacy study (Neurim 112006) was submitted to support the extension of duration of use of Circadin. Two study reports were prepared from this study and included in this submission. The study report produced for the FDA included assessment of sleep latency, and the effects of age (65 - 80 years) and endogenous melatonin levels on sleep latency. The study report prepared for the EMA analysed efficacy primarily for a different age set (over 55 years) and provided efficacy data to 13 weeks.

Neurim 112006 was a randomised, double-blind, placebo-controlled study in adults aged from 18 to 80 years suffering from primary insomnia according to the DSM-IV criteria and with sleep latency of at least 20 minutes. Subjects received placebo for 2 weeks and were then randomised to receive double-blind Circadin or placebo nightly for 3 weeks. Randomisation was stratified by trial site, melatonin levels (high/ low) and age. In the extension phase of this study continuing subjects were either continued on blinded Circadin or, if initially randomised to placebo, were re-randomised to either Circadin or placebo. Blinding was maintained and treatment continued for a further 26 weeks.

There were two primary objectives:

1. To compare change from baseline in subjective sleep latency (as recorded in a sleep diary) in all patients aged 65 – 80 years and change from baseline in subjective sleep maintenance, that is, the number of times being awakened during the night as recorded in the sleep diary in low melatonin excretors aged 18 – 80 years after 3 weeks of double-blind treatment with Circadin 2 mg at night.
2. To compare between treatment group differences in sleep quality, quality of life, subjective sleep latency at Weeks 18 and 26 in patients aged 55 – 80 years and to assess withdrawal effect after discontinuation.

In keeping with the two objectives of this study there were two primary measures of efficacy. The first was the change in baseline in sleep latency as recorded in the sleep diary after 3 weeks of double blind treatment in "low excretors" of melatonin aged 18 – 80 years. The other primary efficacy measure was the number and percentage of subjects aged 55 – 80 years at Visits 6 and 7 (Weeks 23 and 31) with a mean PSQI global score of 6 or less and an improvement from baseline of at least 10% in the mean WHO-5 index, that is, subjects with a treatment response.

Secondary efficacy measures included change from baseline in sleep latency in all patients aged 65 – 80 years and change from baseline in sleep maintenance in low melatonin excretors aged 18 – 80 years after 3 weeks of double-blind treatment. Multiple exploratory analyses were also performed including analyses of sleep latency and responder rates at Weeks 13 and 29. These analyses were provided in response to EMA questions. Mixed-Effects Model Repeated Measure (MMRM) analysis of the ITT population was performed for post hoc assessments of efficacy.

The primary efficacy results of most relevance for the proposed amendment to the indications being sought in Australia are the responder rates in subjects aged over 55 years in the extension phase of the study. Differences in responder rates for this group (ITT group) are shown in Table 1. At Visits 3, 4, 5 and 7 responder rates were higher in subjects given Circadin compared with placebo by from 2.6% (at Visit 7) to 10.8% (at Visit 5). Only the Visit 5 results (Week 15 of study) were statistically significant. At Visit 6 (Week 23) there was a small difference favouring placebo over Circadin. For subjects aged 55 – 80 years the WHO-5 index alone showed a statistically significant differences between Circadin and placebo only for Week 31 (Visit 7) however there was a persistent trend towards slightly lower scores for subjects given Circadin at all time points except Visit 3 where the difference was 0.03, favouring placebo on a scale from 0 – 25 (Table 3). The response rates at Visit 6 and at Visit 7 did not show a statistically significant difference between Circadin and placebo.

Exploratory analysis of results at Weeks 13 and 29 using MMRM showed a statistically significant result at Week 13 for responder rates of 94/365 (25.8%) for the Circadin group and 18/115 (15.7%) for the placebo group in the 55 to 80 year age group (OR 2.09[ 95%CI 1.23, 3.55]; p=0.006) (Table 9). At Week 29 the responder rates were not statistically significant. An overall responder rate that included all time points assessed, the Global Treatment Effect reported a statistically significant effect, with Circadin vs Placebo OR 1.4 [95%CI 1.02; 1.93]; p= 0.04).

The current indication for Circadin specifies an effect on quality of sleep. The measures of quality of sleep in this study did not show a statistically significant benefit over placebo at any of the time points assessed using either the sleep diary or the PSQI global scores. There was however a small but consistent effect favouring Circadin at all time points assessed as shown in Table 4.

Sleep latency was analysed for subjects aged from 55 – 80 years. For this group there was a statistically significant difference of 7.8 minutes favouring Circadin at Week 3 (Table 6). This difference did not remain statistically significant at Week 9 (difference favouring Circadin 5.8 minutes) (Table 7) but was statistically significant at Weeks 10 (Table 8), 18 and 26 as assessed by the sleep diary. Results for the 55 – 80 years subgroup for treatment response favoured Circadin at all visits except Week 23 but were statistically significant only at Weeks 5 and 15. Multiple results were reported for other subgroups and endpoints included in this study.

### Safety

New safety data were available from study 12545A, a post-marketing surveillance study as well as from study 112006 and a new safety summary incorporating previously evaluated studies was submitted. Study 12545A examined discontinuation, withdrawal and rebound effects. The main endpoints were sleep quality and morning alertness, both assessed on a 5 point scale from very good to very bad, and adverse events. Subjects were assessed while taking Circadin, immediately on stopping and within weeks of stopping. Of note, at least 11.4% of subjects took other medication for insomnia while taking Circadin. No significant withdrawal effects were apparent.

Assessment of the adverse effects from the two submitted studies has not shown any new adverse effects of concern. Circadin in use up to 6 months appears to be extremely safe and melatonin has a long history of widespread use over many years, though reporting of adverse events in the post-market phase is likely to have been limited, particularly in those countries where melatonin is available in over-the-counter products.

## Risk Management Plan

There was no requirement for a Risk Management Plan evaluation in a submission of this type.

## Risk-Benefit Analysis

### Delegate Considerations

In the efficacy study for this submission, Neurim 112006, there were multiple endpoints as the study attempted to satisfy both European and US regulators. None of the primary endpoints are ideal to support the proposed extension in duration of use of Circadin from 3 to 13 weeks. The primary endpoint which most closely approaches this is the "responder rate". This was a composite endpoint that included two rating scales assessed at two time points. This use of a combination of scales and time points makes it difficult to clearly see the extent of difference Circadin has made to the majority of subjects for whom it is currently indicated. Nevertheless, a statistically significant effect of Circadin on responder rates was demonstrated for time points beyond the duration of use that has been proposed and for the exploratory analyses at Week 13 and the overall analysis of time points. In addition the quality of sleep indicator trended towards efficacy at every time point assessed in the population for whom Circadin is indicated in Australia.

Results for the multiple components of the primary endpoints and for the secondary endpoints suggest a small reduction in sleep latency and a detectable improvement in function. These endpoints and the composite endpoints reached statistical significance at some time points and approached significance at most points at which they were measured. The current indication specifies the effect of Circadin is on quality of sleep rather than sleep latency. Statistically significant superiority of Circadin over placebo for measures of sleep quality was not demonstrated.

It is clear that Circadin has a degree of ongoing efficacy beyond the currently approved 3 weeks. Dependence is not an issue which makes this product very useful as other approved treatments are associated with varying degrees of dependence.

The Delegate proposed to approve the requested amendment to the indications of *Monotherapy for the short term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over* subject to amendment to the PI to more fully describe the new efficacy study. The advice of the Advisory Committee on Prescription Medicines (ACPM), which has succeeded ADEC, was requested on whether the indications should permit use longer than 3 weeks, particularly given the complex and multiple endpoints measured and the limited demonstration of efficacy in the study to support the proposed change to the indication.

### Response from Sponsor

The sponsor indicated that the objective of the current application was to allow use of Circadin in Australia beyond the currently limited 3 weeks. Insomnia is often long-lasting, especially in the elderly and thus often treated in clinical practice with hypnotics for long periods, although concerns of safety and potential dependence issues have led to restrictions in the permitted treatment duration to ultra short periods for 2 to 4 weeks. Thus, there is a medical need for a safe and efficacious product that can be used for periods in excess of 4 weeks.

The new data for Circadin submitted with this application focuses on the 3-month results, which clearly demonstrate that the response at the end of 3 weeks is enhanced by the end of the 3 months. Furthermore, there are no safety issues or concerns on withdrawal and rebound effects for up to 6 months. Therefore, the risk benefit assessment of using Circadin for primary insomnia, favours the revision of treatment duration up to 3 months (13 weeks).

The analyses of main interest for the Australian application are the pre-planned analyses performed on the target approved population in Australia (over 55 years population) over a 6-month period. In the EU Clinical Study Report (CSR) it uses the stringent double responder rate analysis (quality of

sleep and daytime functioning expressed by - PSQI < 6 and 10% improvement on WHO-5) as a primary parameter and sleep latency, quality of sleep, quality of life and withdrawal effects as secondary endpoints, using the PSQI as a primary scale and the WHO-5 and Tyrer as secondary scales in the over 55 years who completed the 6 months period. In the US CSR the over 55 years population was analysed to look at all variables during the 3 weeks, 3 months and over the 6 months period.

The Delegate proposed to approve the requested amendment to the indications of *Monotherapy for the short term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over* subject to amendment to the PI to more fully describe the new efficacy study.

The sponsor concurred with the Delegate's recommendation. However the sponsor wished to address several key issues raised by the Delegate for ACPM consideration.

The Delegate commented that "The measures of quality of sleep in this study did not show a statistically significant benefit over placebo at any of the time points assessed using either the sleep diary or the PSQI global score".

The PSQI was the primary tool used for the EU study report, and was also used for the double responder analysis. It was the primary tool for sleep quality measurement. The measures of sleep quality do in fact show statistically significant effects of Circadin when looking at the global PSQI. There was a statistically significant effect at Week 3 (p=0.015) and Week 13 (p=0.017), and trends positively at Week 9 (Visit 4) using the pre-planned MMRM analysis. Statistically significant outcomes for PSQI Global Score at Week 3 (p=0.003) and Week 13 (p=0.014) respectively using the pre-planned ANCOVA analysis were also demonstrated.

For the EU study, as mentioned above, the sponsor chose to look at a double responder pre-defined parameter quality of sleep and daytime functioning expressed by - PSQI < 6 and 10% improvement on WHO-5. The rate of double responders with Circadin compared to placebo after 3, 9 and 13 weeks of double blind treatment (post-hoc analysis) was statistically significant at both the 3 and 13 week time points, and was trending positively at Week 9.

Thus, the rate of responders as defined by the double-responder EU variable increased during 3 weeks to 3 months of treatment, suggesting that some patients (about 10%) may need more than 3 weeks to attain a response.

Further to the above, the sponsor clarified why this double responder (PSQI of <6; WHO-5 110% of baseline) analysis was used. The approach was taken in response to the EMA requirement for consistency with the LSEQ analysis (to demonstrate clinical relevant effects in both quality of sleep and daytime functioning), that was used for the original 3-week pivotal study, but which wasn't appropriate for longer periods than 3 weeks. The results serve not only to support efficacy to 3 months but also confirm the existing 3-week LSEQ data already approved by the TGA.

Moreover, there is a clear effect on other parameters based on single scales at specific time points: 3 weeks (confirming the existing data supporting the TGA approved efficacy), 13 weeks (supporting the suggested indication and dose regimen) and 26 weeks (supporting long term efficacy): all pre-planned analyses.

The sponsor also commented on secondary variables.

The data presented above relates to the primary objectives of the EU submission. The primary objective of the US submission and the secondary objective in the EU submission was sleep latency. Sleep latency is considered to be a major parameter of sleep (difficulty initiating sleep is one of the criteria of primary insomnia according to DSM-IV), and therefore relevant to the overall risk benefit analysis. An improvement in response with time was demonstrated for sleep latency in the over 55 years subpopulation. Clear evidence of an increase in response beyond the 3 weeks treatment and up to 3 months and maintenance of the effect over the 6 months period was

demonstrated by many variables and tools. During the sponsor's discussions with the EMA the sponsor was asked to perform responder analyses in order to understand whether the evolution in the effect size was caused by additional patients who responded to the drug. Responder rate analysis is recommended to establish the clinical relevance of the observed effects and to see if the observed progression of the effect is due to extra patients who responded to the drug beyond the 3 weeks.

The proportion of patients showing response (responder is a patient that improves from baseline to 30 minutes or less in Sleep Latency (PSQI Q2)) increased from 29.2% after 3 weeks to 45.1% after 3 months treatment suggesting that some patients may need more than 3 weeks to attain a response. These results are also consistent with the primary double responder analysis showing that the proportion of patients that showed a response increased from 3 weeks to 3 months whether defined by sleep latency, or the double-responder EU primary.

As mentioned above, quality of sleep as measured by the Global PSQI has improved significantly at 13 weeks. Quality of life measured by the WHO-5 was trending positively at 13 weeks. It should be noted that quality of life (WHO-5 Index) was significantly improved over the 26 weeks in the Circadin group compared with placebo, demonstrating that this parameter improved gradually with time. This gradual improvement with time in quality of life might also be linked with the excellent safety profile of Circadin over the 6 months period summarised briefly below.

In study 112006, a high safety profile was demonstrated both during the short-term (up to 3 months) and long-term period (up to 6 months) with less patients having adverse events during the 6 months period in the Circadin group as compared to placebo with no withdrawal and rebound effects. There was no evidence of a difference between treatment groups in the proportion of patients experiencing new symptoms on the Tyrer questionnaire after the withdrawal period, which was about 28% in both groups.

In study 12545A, a PMS study evaluating withdrawal and rebound effect as a primary endpoint, no withdrawal and rebound effect were demonstrated. It should be noted that most of the patients that used benzodiazepines or benzodiazepine derivatives before Circadin treatment were not using them after discontinuation of Circadin and nearly all de novo patients did not try benzodiazepines or benzodiazepine derivatives after discontinuation of Circadin. This is of special importance in view of the clear concerns of safety and potential dependence issues related to other hypnotics.

The safety profile of Circadin is particularly important in the light of concerns about the safety and potential dependency of other treatments for insomnia in Australia.

### Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission for an extension of indications and a variation in dosage and administration for the indication:

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

In making this recommendation, the ACPM considered that the safety of melatonin had been clearly demonstrated although efficacy was modest and variable. There was, however, some efficacy demonstrated from Weeks 3 to 13 and it was therefore proposed to recommend approval for treatment for this period.

Changes to the Product Information (PI) and Consumer Medicines Information (CMI) recommended prior to approval include:

Amendments to the Clinical Trials section to ensure the full disclosure of the details of the new study (Neurim 112006) particularly in relation to efficacy only demonstrated in a limited patient age group and duration of treatment.

### Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Circadin containing melatonin 2mg for the new indication as shown below, dosage and administration and other PI changes:

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

## *Attachment 1. Product Information*

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

# Product Information

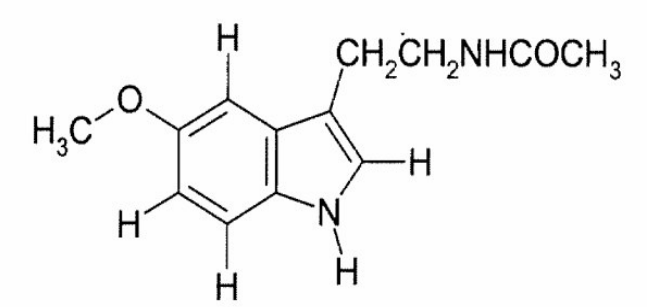
# Circadin® Prolonged Release Tablets

## *Name of the medicine*

Melatonin

Chemical name: N-[2-(5-Methoxyindol-3-yl)ethyl]acetamide. Melatonin is a slightly off-white, odourless crystalline powder.

Structural formula:




Molecular formula: $C_{13}H_{16}N_2O_2$
Molecular weight: 232.27
CAS number: 73-31-4
pKa: 12.3 – 12.7

## *Description*

The active ingredient in Circadin prolonged release tablets is a melatonin NOT of plant or animal origin. Circadin prolonged release tablets also contain the excipients: Ammonio methacrylate copolymer, calcium hydrogen phosphate, lactose, colloidal anhydrous silica, purified talc and magnesium stearate. Melatonin is very slightly soluble in water and in dilute hydrochloric acid.

## *Pharmacology*

Pharmacotherapeutic group: Melatonin Receptor Agonists, ATC code: N05CH01

### Pharmacological actions:

Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin. Physiologically, melatonin secretion increases soon after the onset of darkness, peaks at 2-4 am and diminishes during the second half of the night. Melatonin is associated with the control of circadian rhythms and

entrainment to the light-dark cycle. It is also associated with a hypnotic effect and increased propensity for sleep.

*Mechanism of action*
The activity of melatonin at the MT1 MT2 receptors is believed to contribute to its sleep-promoting properties via their distinct actions on the circadian clock. The MT1 receptors are thought to inhibit neuronal firing, while the MT2 receptors have been implicated in the phase-shifting response.

*Rationale for use*
Because of the role of melatonin in sleep and circadian rhythm regulation, and the age related decrease in endogenous melatonin production, melatonin may effectively improve sleep quality particularly in patients who are over 55 with primary insomnia.

## Pharmacokinetics:

The absolute bioavailability of melatonin from CIRCADIN has not been assessed. Other oral formulations of melatonin have an absolute bioavailability in the region of 15% but this is highly variable with high first-pass metabolism. The relative bioavailability of melatonin from CIRCADIN is comparable to that of an oral melatonin solution.

Data from other formulations of melatonin indicate that the absorption of orally ingested melatonin is complete in adults and may be decreased by up to 50% in the elderly. The kinetics of melatonin is linear over the range of 2-8 mg as obtained from published results using a formulation other than CIRCADIN.

Bioavailability as assessed from other oral formulations of melatonin is in the order of 15%. There is a significant first pass effect with an estimated first pass metabolism of 85% as assess from other oral formulations of melatonin. $T_{max}$ occurs after 2.6 hours in a fed state. The rate of melatonin absorption following Circadin 2 mg oral administration is affected by food. The presence of food delayed the absorption of the melatonin resulting in a later $T_{max}$ ($T_{max}$= 2.6 h versus $T_{max}$= 1.6 h). $C_{max}$ and AUC levels were not affected by food.

*Distribution*
The *in vitro* plasma protein binding of melatonin is approximately 60%. Melatonin is mainly bound to albumin, alpha$_1$-acid glycoprotein and high density lipoprotein. The binding to the other serum proteins is insignificant. The melatonin binding was constant over the range of the studied concentrations in serum. Literature data indicates that melatonin is distributed in all body fluids and is accessible at all tissues.

*Biotransformation*
Experimental data suggest that isoenzymes CYP1A1, CYP1A2 and possibly CYP2C19 of the cytochrome P450 system are involved in melatonin metabolism. The principal metabolite is 6-sulphatoxy-melatonin (6-S-MT), which is inactive. The site of biotransformation is the liver. The excretion of the metabolite is completed within 12 hours after ingestion.

*Elimination*
Terminal half life ($t_{½}$) is 3.5-4 hours. Elimination is by renal excretion of metabolites, 89% as sulphated and glucoronide conjugates of 6-hydroxymeltonin and 2% is excreted as melatonin (unchanged drug).

*Gender*

A 3-4-fold increase in $C_{max}$ is apparent for women compared to men. A five-fold variability in $C_{max}$ between different members of the same sex has also been observed.

However, no pharmacodynamic differences between males and females were found despite differences in blood levels.

*Elderly*

Melatonin metabolism is known to decline with age. Across a range of doses, higher AUC and Cmax levels have been reported in older subjects compared to younger subjects, reflecting the lower metabolism of melatonin in the elderly. $C_{max}$ levels around 500 pg/ml in adults (18-45) versus 1200 pg/ml in the elderly (55-65); AUC levels around 3,000 pg*h/mL in adults versus 6000 pg*h/mL in the elderly.

*Renal impairment*

Melatonin did not accumulate after repeated dosing with CIRCADIN. This finding is compatible with the short half-life of melatonin in humans.

The levels assessed in the blood of patients at 23:00 (2 hours after administration) following 1 and 3 weeks of daily administration were 411.4 ± 56.5 and 432.00 ± 83.2 pg/ml respectively, and are similar to those found in healthy volunteers following a single dose of Circadin 2 mg.

*Hepatic impairment*

The liver is the primary site of melatonin metabolism and therefore, hepatic impairment results in higher endogenous melatonin levels.

Plasma melatonin levels in patients with cirrhosis were significantly increased during daylight hours. Patients had a significantly decreased total excretion of 6-sulfatoxymelatonin compared with controls.

## *Clinical trials*

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.

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.

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.

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.

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 adifference 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=0.006).
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.

Long term safety: The safety profile both during 3 weeks and during the 26 week periods was comparable to placebo with no withdrawal and rebound effects.

In an open study where 96 subjects completed 12 months treatment with Circadin no tolerance, rebound or withdrawal effects were reported.

## Indications

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

## Contra-indications

Circadin prolonged release tablets are contraindicated in patients with a known hypersensitivity to any ingredient of the product (see DESCRIPTION).

## Precautions

***Drowsiness:*** Circadin may cause drowsiness. Therefore the product should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety.

***Effects on ability to drive and operate machinery:*** Circadin has negligible influence on the ability to drive and use machines. Nevertheless, patients should avoid engaging in hazardous activities (such as driving or operating machinery) after taking Circadin.

***Autoimmune diseases:*** No clinical data exist concerning the use of Circadin in individuals with autoimmune diseases. Therefore Circadin is not recommended for use in patients with autoimmune diseases.

***Excipients:*** The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine.

***Effects on fertility:*** No significant effects on fertility or reproductive performance were observed in rats given oral melatonin prior to mating through to early gestation at doses over 900-fold the recommended clinical dose, based on body surface area.

***Use in pregnancy:***
**Category B3.**

No significant effects on embryofetal 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.

***Use in lactation:***
Maternal transfer of exogenous melatonin to the fetus via the placenta or milk has been demonstrated in several animal species including rats, hamsters, goats, monkeys and cows. A slight reduction in post-natal growth, viability and development was found in rats given oral melatonin during gestation through weaning at doses over 900-fold the recommended clinical dose, based on body surface area; the no-effect dose was over 250-fold the clinical dose.

Endogenous melatonin has been detected in human breast milk, thus exogenous melatonin is likely excreted into human milk. The effects of melatonin on the nursing infant have not been established. Therefore, breast-feeding is not recommended in women under treatment with melatonin.

***Paediatric use:***
Circadin is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy.

***Use in the elderly:***
Melatonin metabolism is known to decline with age. Across a range of doses, higher AUC and $C_{max}$ levels have been reported in older subjects compared to younger subjects, reflecting the lower metabolism of melatonin in the elderly.

***Carcinogenicity***
An oral lifetime carcinogenicity study with melatonin in rats showed an increased incidence of thyroid follicular cell adenomas in males at doses around 700-fold the recommended clinical dose, based on body surface area. No neoplastic tissue histopathology was examined at lower doses and therefore the no-effect dose could not be determined. These effects were associated with liver enzyme induction in this species and are unlikely to be relevant to humans.

***Genotoxicity:***
Results from a standard battery of *in vitro* and *in vivo* assays showed no evidence of a genotoxic potential for melatonin.

***Interactions with other medicines:***

Pharmacokinetic interactions

***Hepatic enzymes -*** Melatonin has been observed to induce CYP3A *in vitro* at supra-therapeutic concentrations. The clinical relevance of the finding is unknown. If induction occurs, plasma concentrations of concomitantly administered drugs can be reduced.

Melatonin does not appear to induce CYP1A enzymes *in vitro* at supra-therapeutic concentrations. Therefore, interactions between melatonin and other active substances as a consequence of melatonin's effect on CYP1A enzymes are not likely to be significant.

Melatonin's metabolism is mainly mediated by CYP1A enzymes. Therefore, interactions between melatonin and other active substances as a consequence of their effect on CYP1A enzymes is possible:

***Quinolones -*** CYP1A2 inhibitors such as quinolones may give rise to increased melatonin exposure.

***Carbamazepine and rifampicin -*** CYP1A2 inducers such as carbamazepine and rifampicin may give rise to reduced plasma concentrations of melatonin.

***Fluvoxamine -*** Caution should be exercised in patients on fluvoxamine, which increases melatonin levels (17-fold higher AUC and 12-fold higher serum $C_{max}$) by inhibiting its metabolism by hepatic cytochrome P450 (CYP) isozymes CYP1A2 and CYP2C19. The combination should be avoided.

***5- or 8-methoxypsoralen -*** Caution should be exercised in patients on 5- or 8-methoxypsoralen (5 and 8-MOP), which increases melatonin levels by inhibiting its metabolism.

***Cimetidine -*** Coadministration of CIRCADIN with cimetidine resulted in a 1.7 fold increase in exposure to melatonin with no change in the exposure to cimetidine. Caution should be exercised in patients on cimetidine, a CYP2D inhibitor which increases plasma melatonin levels by inhibiting its metabolism.

***Cigarette smoking -*** Cigarette smoking may decrease melatonin levels due to induction of CYP1A2.

***Oestrogens -*** Caution should be exercised in patients on oestrogens (e.g. contraceptives or hormone replacement therapy), which increase melatonin levels by inhibiting its metabolism by CYP1A1 and CYP1A2.

***Other -*** There is a large amount of data in the literature regarding the effect of adrenergic agonists/antagonists, opiate agonists/antagonists, antidepressant medicinal products, prostaglandin inhibitors, benzodiazepines, tryptophan and alcohol, on endogenous melatonin secretion. Whether or not these active substances interfere with the dynamic or kinetic effects of Circadin or vice versa has not been studied.

Pharmacodynamic interactions

***Alcohol -*** Alcohol should not be taken with Circadin, because it reduces the effectiveness of Circadin on sleep. The prolonged release characteristics of Circadin may be altered by alcohol, resulting in immediate release of melatonin.

***Hypnotics -*** Circadin may enhance the sedative properties of benzodiazepines and non-benzodiazepine hypnotics, such as zaleplon, zolpidem and zopiclone. In a clinical trial, there was clear evidence for a transitory pharmacodynamic interaction between Circadin and zolpidem one hour following co-dosing. Concomitant administration resulted in increased impairment of attention, memory and co-ordination compared to zolpidem alone.

***Thioridazine and imipramine -*** Circadin has been co-administered in studies with thioridazine and imipramine, active substances which affect the central nervous system. No clinically significant pharmacokinetic interactions were found in each case. However, Circadin co-administration resulted in increased feelings of tranquility and difficulty in performing tasks compared to imipramine alone, and increased feelings of "muzzy-headedness" compared to thioridazine alone.

***Effect on laboratory tests:***
No information is available on the effect of melatonin on laboratory tests.

## *Adverse Effects*

In clinical trials (in which a total of 1931 patients were taking Circadin and 1642 patients were taking placebo), 48.8% of patients receiving Circadin reported an adverse reaction compared with 37.8% taking placebo. Comparing the rate of patients with adverse reactions per 100 patient weeks, the rate was higher for placebo than Circadin (5.743 - placebovs. 3.013 - Circadin). The most common adverse reactions were headache, nasopharyngitis, back pain, and arthralgia, which were common, by MedDRA definition, in both the Circadin and placebo treated groups. In the Circadin group, there were 72 cases (2.9% of the safety population) of adverse events leading to discontinuation of the patient. In the placebo group there were 62 cases (4.0% of the safety population) of adverse events leading to discontinuation of the patient.

**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 disoprders | | |
| Anxiety | 1.0 | 1.2 |
| Respiratory, thoratic and mediastinal disorders | | |
| Cough | 2.2 | 1.3 |
| Pharyngolaryngeal pain | 1.5 | 0.9 |
| Rhinitis | 1.1 | 0.9 |

The adverse reactions in the table below were reported in clinical trials and were defined as possibly, probably or definitely related to treatment. A total of 9.5% of subjects receiving Circadin reported an adverse reaction compared with 7.4% of subjects taking placebo. Only those adverse events occurring in subjects at an equivalent or greater rate than placebo have been included.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common (≥ 1/10); Common (≥ 1/100 to <1/10); Uncommon (≥ 1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very rare (<1/10,000), Not known (cannot be established from the available data).

**Adverse events related to treatment occurring with a frequency < 1%**

| System Organ Class | Uncommon | Rare |
|---|---|---|
| Infections and Infestations | | Herpes zoster |
| Blood and Lymphatic System Disorders | | Leukopenia, Thrombocytopenia |
| Cardiac Disorders | | Angina Pectoris, Palpitations |
| Metabolism and Nutrition Disorders | | Hypertriglyceridaemia, Hypocalcaemia, Hyponatraemia |
| Psychiatric Disorders | Irritability, Nervousness, Restlessness, Insomnia, Abnormal dreams, Anxiety | Mood altered, Aggression, Agitation, Crying, Stress Symptoms, Disorientation, Early morning awakening, Libido increased, Depressed mood, Depression |
| Nervous System Disorders | Migraine, Lethargy Psychomotor hyperactivity, Dizziness, Somnolence | Syncope, Memory impairment, Disturbance in attention, Dreamy state, Restless Legs Syndrome, Poor quality sleep, Paresthesia |
| Eye Disorders | | Visual acuity reduced, Vision blurred, Lacrimation increased |
| Ear and Labyrinth Disorders | | Vertigo positional, Vertigo |
| Vascular Disorders | | Hot flush |
| Gastrointestinal Disorders | Abdominal pain, Abdominal pain upper, Mouth Ulceration, Dry mouth | Gastrooeshophageal Reflux Disease, Gastrointestinal disorder, oral Mucosal Blistering, Tongue Ulceration, Gastrointestinal upset, Vomiting, Bowel sounds abnormal, Flatulence, Salivary hypersecretion, Halitosis, Abdominal Discomfort, Gastric disorder, Gastritis |
| Hepatobiliary Disorders | Hyperbilirubinaemia | |
| Skin and Subcutaneous Tissue Disorders | Dermatitis, Night Sweats, Pruritus, Rash, Pruritus Generalised, Dry Skin | Eczema, Erythema, Hand Dermatitis, Psoriasis, Rash Generalised, Rash pruritic, , Nail disorder |
| Musculoskeletal and Connective Tissue Disorders | Pain in extremity | Arthritis, Muscle, Neck pain, Night cramps |
| Reproductive System and Breast Disorders | Menopausal symptoms | Priapism Prostatis |
| General Disorders and Administration Site | Asthenia, Chest Pain | Fatigue, Pain, Thirst |

| | | |
|---|---|---|
| Conditions | | |
| Renal and Urinary Disorders | Glycosuria, Proteinuria | Polyuria, Hematuria, Nocturia |
| Investigations | Liver Function Test Abnormal, Weight increased | Hepatic enzyme increased, Blood Electrolytes Abnormal, Laboratory Test Abnormal |

## *Dosage and Administration*

Oral use. Tablets should be swallowed whole.

The recommended dose is 2 mg once daily, 1-2 hours before bedtime and after food. This dosage may be continued for up to thirteen weeks.

*Paediatric use*

Circadin is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy.

*Renal insufficiency*

The effect of any stage of renal insufficiency on melatonin pharmacokinetics has not been studied. Caution should be used when melatonin is administered to such patients.

*Hepatic impairment*

There is no experience of the use of Circadin in patients with liver impairment. Published data demonstrates markedly elevated endogenous melatonin levels during daytime hours due to decreased clearance in patients with hepatic impairment. Therefore, Circadin is not recommended for use in patients with hepatic impairment.

## *Overdosage*

In general, the main therapy for all overdoses is supportive and symptomatic care.

Symptoms

No case of overdose has been reported. Circadin has been administered at 5 mg daily doses in clinical trials over 12 months without significantly changing the nature of the adverse reactions reported.

Administration of daily doses of up to 300 mg of melatonin without causing clinically significant adverse reactions have been reported in the literature.

If overdose occurs, drowsiness is to be expected.

Treatment

Clearance of the active substance is expected within 12 hours after ingestion. No special treatment is required

For further advice on management of overdose please contact the Poisons Information Centre (Tel: 13 11 26 for Australia and Tel: 0800 764 766 for New Zealand).

## *Presentation and storage conditions*

### Presentation

Circadin 2 mg prolonged release tablets: White to off-white, round, biconvex tablets in blister packs of 21. AUST R 153959

### Storage conditions

Store below 25ºC. Protect from light

## *Name and address of the sponsor*

**Sponsor:**
RAD Data Australia Pty Ltd
Level 7, Suite 2, 100 Walker St
North Sydney, NSW 2060

**Distributor:**
Sigma Pharmaceuticals (Australia) Pty Ltd
96 Merrindale Drive
Croydon VIC 3136
Ph: 1300 656 755

## *Poisons schedule of the medicine*

S.4.

## *Date of approval:*

04 January 2011

CIRCADIN is a registered trademark of Neurim Pharmaceuticals