New Zealand Data sheet

1 CIRCADIN®

Melatonin 2 mg Prolonged Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient in CIRCADIN prolonged release tablets is a melatonin NOT of plant or animal origin.

Excipient with known effect: lactose monohydrate.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

CIRCADIN 2 mg prolonged release tablets: White to off-white, round, biconvex tablets in blister packs of 21 and 30.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of 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.

4.3 Contraindications

CIRCADIN prolonged release tablets are contraindicated in patients with a known hypersensitivity to any ingredient of the product (see section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION and section 6.1 List of excipients).

4.4 Special warnings and precautions for use

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.

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.

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.

4.5 Interaction with other medicines and other forms of interaction

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 medicines 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 zalepon, 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.

Effects on Laboratory Tests

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

4.6 Fertility, pregnancy and lactation

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 embryofoetal development were observed in rats given oral melatonin during the period of organogenesis at doses over 900 - fold the recommended clinical dose, based on body surface area.

No clinical data on exposed pregnancies are available. In view of the lack of clinical data, use in pregnant women and by women intended to become pregnant is not recommended.

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.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable 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 – placebo vs. 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

Body System/Adverse Experience	Circadin % (N=1931)	Placebo % (N=1642)
Headache	5.7	6.2
Migraine	1.1	1.2
Psychiatric disorders		
Anxiety	1.0	1.2
Respiratory, thoracic and mediastinal disorders		
Cough	2.2	1.3
Pharyngolaryngeal pain	1.5	0.9
Rhinitis	1.1	0.9

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	Not known
Infections and Infestations		Herpes zoster	
Blood and Lymphatic System Disorders		Leukopenia, Thrombocytopenia	
Cardiac Disorders		Angina pectoris Palpitations	
Immune System Disorders			Hypersensitivity reaction
Metabolism and Nutrition Disorders		Hypertriglyceridaemia Hypocalcaemia Hyponatraemia	
Psychiatric Disorders	Irritability, Nervousness, Restlessness, Insomnia, Abnormal dreams, Anxiety, Nightmares	Mood altered, Aggression, Agitation, Crying, Stress symptoms, Disorientation, Early morning awakening, Libido increased,	

System Organ Class	Uncommon	Rare	Not known
		Depressed mood, Depression	
Nervous System Disorders	Migraine Lethargy Psychomotor hyperactivity, Dizziness, Somnolence, Headache	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	Hypertension	Hot flush	
Gastrointestinal Disorders	Abdominal pain, Abdominal pain upper, Dyspepsia, Mouth ulceration, Dry mouth, Nausea	Gastro-oesophageal 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	Angioedema, Oedema of mouth, Tongue oedema
Musculoskeletal and Connective Tissue Disorders	Pain in extremity	Arthritis, Muscle spasm, Neck pain, Night cramps	
Reproductive System and Breast Disorders	Menopausal symptoms	Priapism, Prostatitis	Galactorrhoea
General Disorders and Administration Site Conditions	Asthenia, Chest pain	Fatigue, Pain, Thirst	

System Organ Class	Uncommon	Rare	Not known
Renal and Urinary Disorders	Glycosuria, Proteinuria	Polyuria, Haematuria, Nocturia	
Investigations	Liver function test abnormal, Weight increased	Hepatic enzyme increased, Blood electrolytes abnormal, Laboratory test abnormal	

Post-Marketing Data

Psychiatric Disorders: Nightmares

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

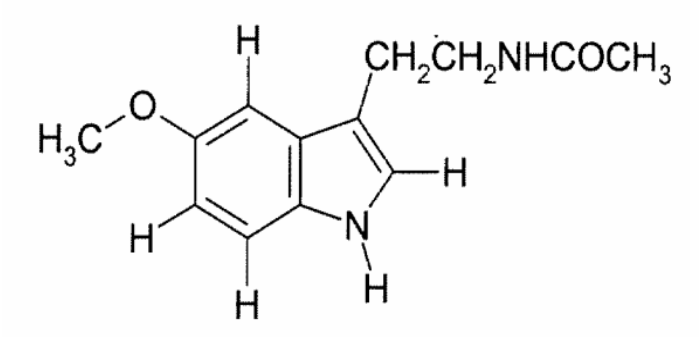
5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Melatonin Receptor Agonists, ATC code: N05CH01

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

Melatonin is very slightly soluble in water and in dilute hydrochloric acid.

5.1 Pharmacodynamic properties

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.

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 a difference from placebo in mean change from baseline in subjective sleep latency, assessed using a sleep diary, of -7.8 minutes after 3 weeks (p = 0.014). Small differences in sleep latency were generally maintained over 13 weeks of placebo-controlled treatment.

The percentage of patients showing both remission of insomnia (PSQI of < 6) and a clinically relevant improvement of 10% in quality of life scores (WHO-5 index) increased from 16.7% (cf. 10.6% placebo, p = 0.044) at week 3 to 25.8% at week 13 (cf. 15.7% placebo, p = 0.0006).

This study also examined the effect of CIRCADIN on sleep latency in younger subjects with primary insomnia and low excretion of melatonin. Clinically significant effects on sleep latency were not demonstrated in these patients.

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.

5.2 Pharmacokinetic properties

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.

Absorption

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 medicine).

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.

5.3 Preclinical safety data

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CIRCADIN prolonged release tablets contain the excipients: Ammonio methacrylate copolymer, calcium hydrogen phosphate dihydrate, lactose monohydrate, colloidal silicon dioxide, purified talc and magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store below 25ºC. Protect from light.

6.5 Nature and contents of container

Blister pack, PVC/PVdC/Al

6.6 Special precautions for disposal

No special requirements for disposal.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Pharmacy Retailing t/a Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Mangere
Auckland
New Zealand

9 DATE OF FIRST APPROVAL

16 June 2011

10 DATE OF REVISION OF THE TEXT

18 March 2019

CIRCADIN is a registered trademark of Neurim Pharmaceuticals

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformat in line with the new form
2; 4; 5; 6	Editorial changes
6.2	Add incompatibility
6.3	Add shelf life
6.5	Add nature of container
9	Add date of first approval