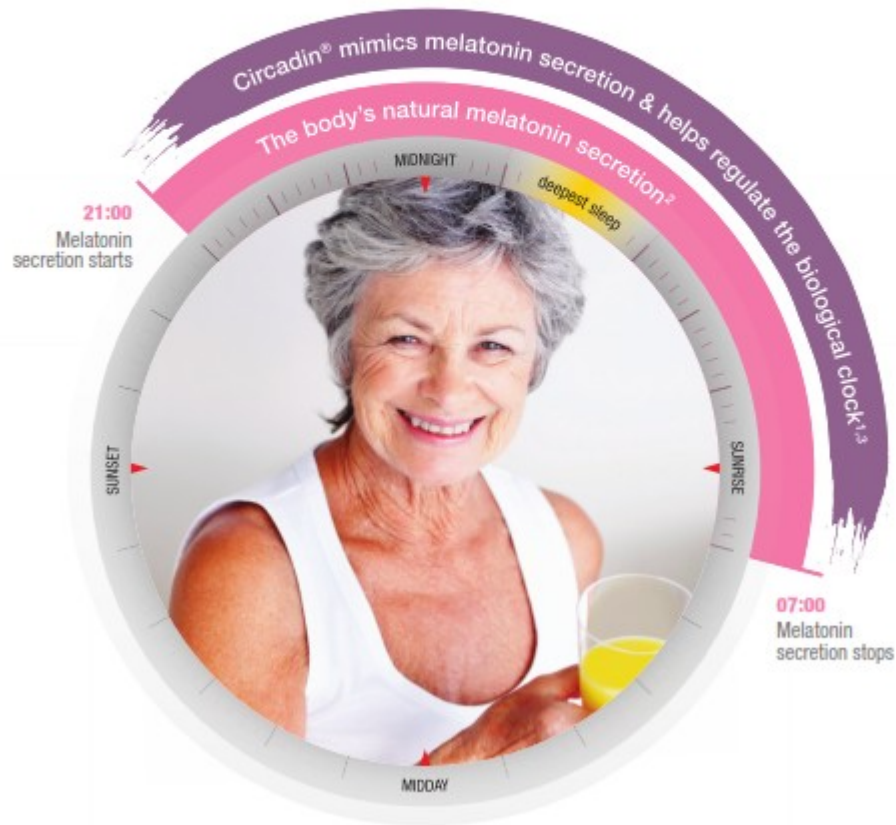


For Restorative Sleep

Timing is Everything.



circadin®
prolonged release melatonin
Sleep well, Live well.

Sleep

SLEEP IS NECESSARY FOR:^{1,2}



Insomnia

Insomnia is a condition of unsatisfactory sleep, either in terms of sleep onset, sleep maintenance or early waking.³

- Insomnia is a common sleep disorder and its prevalence increases with age⁴
- Approximately 50% of the elderly population report insomnia and an overall dissatisfaction with quality of sleep⁴

Insomnia

Poor quality sleep can affect the physical and mental health of sufferers in the following ways:^{4,5}

- Significant daytime distress
- Impaired day time functioning
- Fatigue & mood disturbances
- Cardiovascular disease
- Obesity
- High blood pressure
- Cholesterol

What is Primary Insomnia

Primary insomnia is insomnia not attributable to any known physical or mental condition or environmental cause, and is characterised by a consistent set of symptoms such as;⁶

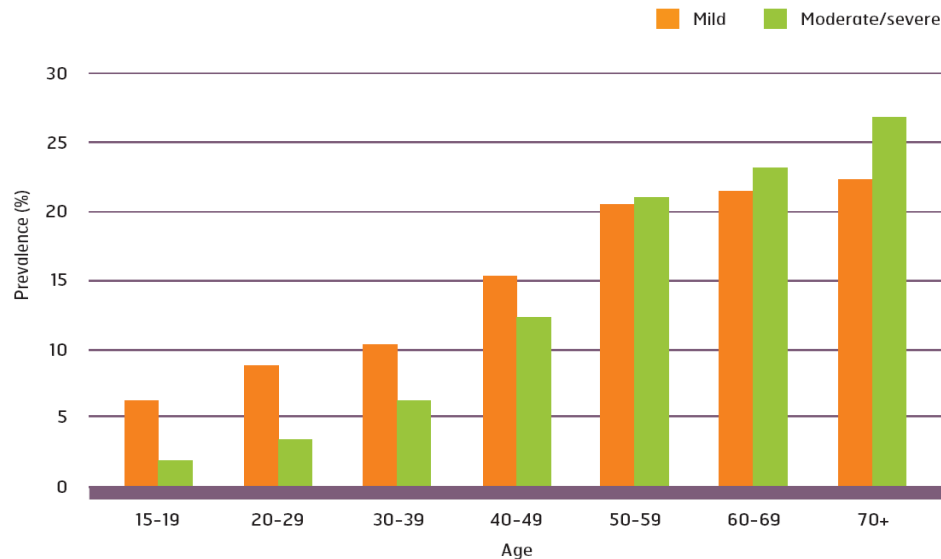
- **Difficulty in falling asleep**
- **Difficulty maintaining sleep**



Rationale for developing Circadin® for

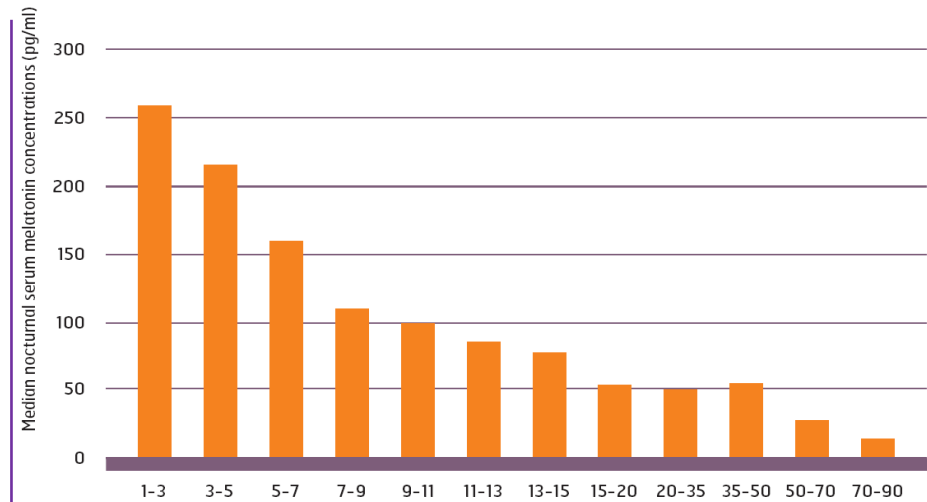
- As we age, the secretion of melatonin in the body declines, which can result in reduced quality of sleep.^{7,8}

Insomnia prevalence increases with age



Adapted from Weyerer S and Dilling H 9

Melatonin secretion decreases as a person ages



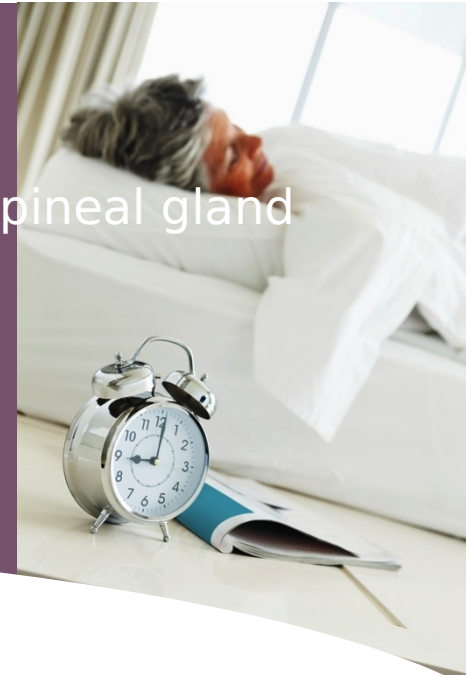
Adapted from Waldhauser F 7

- Approximately 50% of the elderly population report insomnia and an overall dissatisfaction with quality of sleep⁴

What is Melatonin?

Melatonin is¹⁰ a

- a naturally occurring hormone produced by the pineal gland
- an important cue of the internal biological clock
- an important physiological sleep regulator



Circadin® - prolonged release

melatonin¹⁰
First in a
class of
insomnia
treatment

Melatonin
receptor
agonist

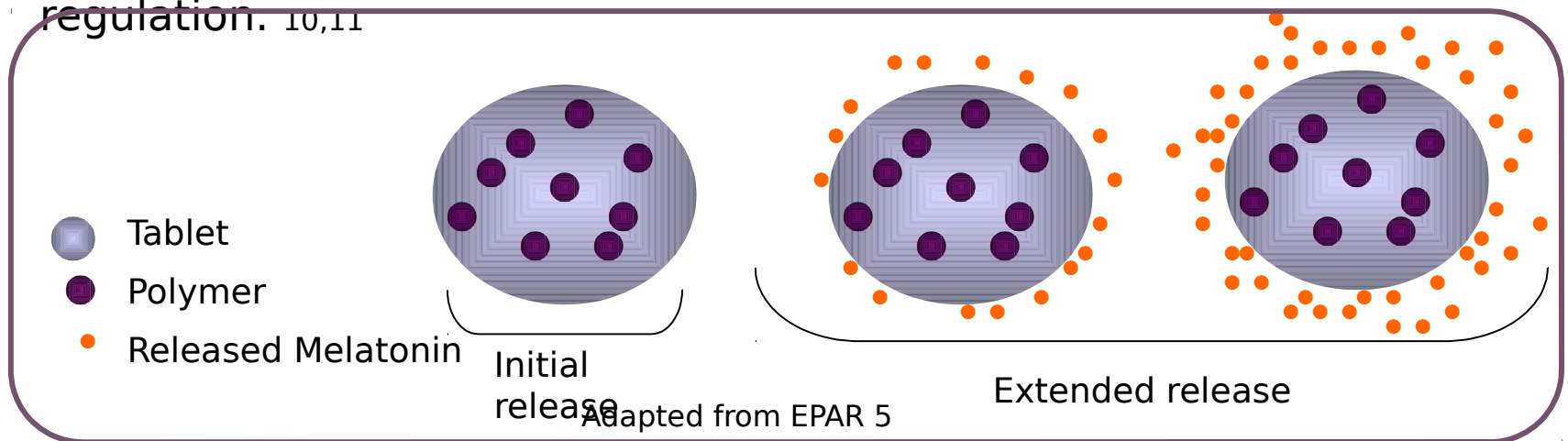
Synthetic
active
ingredient

Registered
and
prescription



Circadin® - Mechanism of action

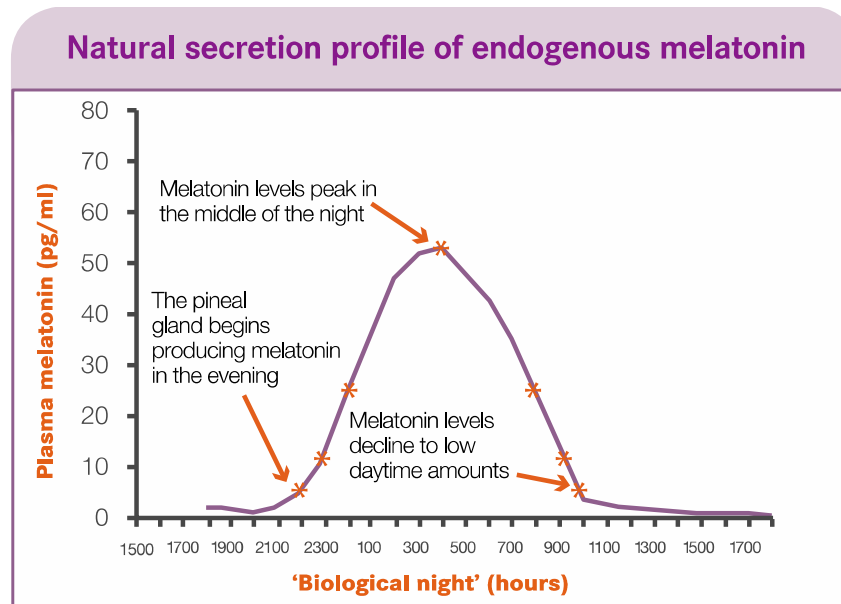
- Circadin is a prolonged-release formulation of melatonin ¹⁰
- It works by selectively binding to melatonin receptors and mimicking the natural physiological profile, helping in sleep and circadian rhythm regulation. ^{10,11}



- Circadin circumvents the fast clearance of the hormone by releasing melatonin in the gut over an extended period of time, thereby mimicking physiological patterns of melatonin secretion ¹²

Circadin® over time

Circadin® mimics the natural melatonin profile by releasing melatonin gradually over 8-10 hours, which helps regulate natural circadian rhythm and provide restorative sleep.¹¹



Adapted from Arendt et al (2005)¹³

Circadin® benefits

- **Does not alter sleep architecture**
- **Improves sleep onset latency¹⁵**
- **Improves quality of sleep¹⁵**
- **Improves daytime functioning & alertness⁴**



Tolerability

Circadin® is well tolerated ¹⁰

- In clinical trials, Circadin had a similar adverse event profile to placebo
- The most common adverse reactions observed in the clinical trials in both the Circadin and placebo groups were headache, nasopharyngitis, back pain and asthenia

Circadin® shows no evidence of rebound insomnia, dependence or withdrawal effects^{4,5,11,13}

Patient Information ¹⁰



PUT INSOMNIA TO BED



Looking for an improved quality of sleep?



Aged 55 or over?



Treatment for primary insomnia

**A goal of a good night's sleep
is to wake up refreshed**

Dosage and administration ^{10,16}

- Recommended dose is 2mg
- Take 1-2 hours before bed and after food
- Swallow the whole tablet
- Continue treatment for at least three weeks for best response

Advice for patients¹⁰

- Circadin® does not have an immediate effect – you should just feel a natural sleepiness and desire to go to bed between 1-2 hours after taking it
- Alcohol may reduce the effectiveness of Circadin® on sleep
- For the best effect on quality of sleep you should take Circadin® at around the same time each day for the full 13 week treatment period and then see your doctor for review



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Sleep Hygiene

- Recommend simple sleep hygiene measures or lifestyle and environmental changes that may help patients sleep

Some examples are

- Improve your sleep environment, such as ensuring the bedroom is warm, quiet and dark.
- Go to bed and wake up at the same time each day, even after a poor night's sleep.
- Do not stay in bed if you are awake for more than 20 minutes; go to another room and do something relaxing

- Be as active as possible during the day and spend time outdoors if possible

- Limit caffeine and alcohol

Patient benefit

Quality
restorative
sleep

Morning
alertness

Improve
d quality
of life

Circadin® helps the body restore its optimal sleep-wake cycle. By promoting quality sleep, patients awake refreshed and alert with improved quality of life ^{4,10,11}

Quick Quiz

1. What is primary insomnia?
2. What is Circadin?
3. How do you take Circadin?
4. What benefits can Circadin offer patients?
5. What sleep hygiene advice can you offer patients?

ABRIDGED PRODUCT INFORMATION

Circadin® (melatonin) 2 mg prolonged release tablets

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

Contraindications: Hypersensitivity to any ingredient in the product.

Precautions: May cause drowsiness. Has negligible influence on the ability to drive and use machines. Not recommended for use in patients with autoimmune diseases. Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine. Not recommended for use in children and adolescents below 18 years of age. Melatonin metabolism is known to decline with age, with higher AUC and C_{max} levels reported in older subjects compared to younger subjects. Caution should be used in those with renal insufficiency. Not recommended for use in patients with hepatic impairment (see full Data Sheet).

Pregnancy (B3): No clinical data on exposed pregnancies are available. Use in pregnant women and by women intended to become pregnant is not recommended.

Lactation: Endogenous melatonin has been detected in human breast 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.

Interactions: Quinolones, carbamazepine, rifampicin, fluvoxamine, 5- or 8-methoxypsoralen, cimetidine, cigarette smoking, oestrogens, adrenergic agonists/antagonists, opiate agonists/antagonists, antidepressants, prostaglandin inhibitors, benzodiazepines, tryptophan, alcohol, zaleplon, zolpidem, zopiclone, thioridazine and imipramine (see full Data Sheet).

Adverse Effects: Common adverse reactions include headache, nasopharyngitis, back pain and arthralgia. See full Data Sheet for complete list.

Dosage: One tablet daily swallowed whole 1-2 hours before bedtime and after food. This dosage may be continued for up to thirteen weeks (see full Data Sheet).

Please review full Data Sheet before prescribing. Data Sheet is available at www.medsafe.govt.nz

Circadin® is an unfunded prescription medicine - a prescription charge will apply.

Circadin® is a registered trademark of Neurim Pharmaceuticals Limited used under licence by Aspen Pharma Pty. (PI last amended 28/06/2011) TAPS PP2924-120C

REFERENCES

1. Zisapel N. Sleep and sleep disturbances: biological basis and clinical implications. *Cell. Mol. Life Sci.* 2007;64:1174-1186
2. Zammit GK et al. Quality of life in people with insomnia. *Sleep* 1999;22(Suppl 2): S379-S385.
3. Wilson SJ et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *Journal of Psychopharmacology* 2010;24(11):1577-1600. 392-398
4. Lemoine P et al. Prolonged-release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects. *J. Sleep Res.* 2007;16:372-380.
5. Hoevenaer-Blom MP; Spijkerman AMW; Kromhout D; van den Berg JF; Verschuren WMM. Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: the MORGEN Study. *SLEEP* 2011;34(11):1487-1492.
6. EPAR, Assessment report for Circadin. Procedure No. EMEA/H/C/695.
7. Waldhauser F et al. Alterations in nocturnal serum melatonin levels in humans with growth and aging. *J Clin Endocrinol Metab.* 1988;66(3): 648-652.
8. Mahlberg R, et al. *Sleep Res* 2009 .
9. Weyerer S and Dilling H. Prevalence and treatment of insomnia in the community: results from the Upper Bavarian Field Study. *Sleep* 1991;14(5).
10. CIRCADIN® Data Sheet.
11. Wade AG et al. Efficacy of prolonged release melatonin in insomnia patients aged 55-80 years: quality of sleep and next-day alertness outcomes. *Current Medical Research & Opinion* 2007;23(10):2597-2605.
12. Lemoine P. Prolonged-release formulation of melatonin (Circadin) for the treatment of insomnia. *Expert Opin. Pharmacother.* [Early Online] 2012
13. Arendt et al. Melatonin as a chronobiotic. *Sleep Med Rev* 2005;9:25-39
14. Luthringer R et al. The effect of prolonged-release melatonin on sleep measures and psychomotor performance in elderly patients with insomnia. *Int Clin Psychopharmacol* 2009;24(5):239-249.
15. Wade A et al. Nightly treatment of primary insomnia with prolonged release melatonin for 6 months: a randomized placebo controlled trial on age and endogenous melatonin as predictors of efficacy and safety. *BMC Medicine* 2010;8:51.
16. Wade AG et al. Prolonged release melatonin in the treatment of primary insomnia: evaluation of the age cut-off for short- and long-term response. *Current Medical Research & Opinion* 2011;27(1):87-98.16.

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