Circadin® Clinical Data

Circadin®, sustained-release melatonin, is a new sleep medication and first in a new class approved for clinical use in the European Union (EU). It is indicated for short-term treatment of primary insomnia, characterised by poor quality of sleep, in patients aged 55 years and above. The regulatory approval of Circadin® for this indication represents a new therapeutic principle in insomnia therapy.

ROLE OF MELATONIN

Melatonin is a hormone produced and secreted by the pineal gland in the brain at night. It is a signal of darkness in humans and acts as the body's own sleep regulator. In humans, a region in the brain known as the suprachiasmatic nucleus acts as the brain's 'clock' by responding to light and dark, thereby giving input to the pineal gland to produce melatonin at night – this is known as a circadian rhythm.

The production of melatonin generally decreases with age and is thought to be linked to increasing insomnia prevalence among the elderly.[1, 2, 3] This relationship has led to the 'melatonin-replacement' hypothesis that treatment with melatonin therapy may replenish the deficiency in the endogenous sleep-regulating hormone and improve sleep.

As endogenous melatonin is produced throughout the night, treatment of disorders that are associated with diminished nocturnal melatonin secretion requires a formulation of the hormone that would reproduce the normal nocturnal pattern of melatonin. Therefore, Circadin® 2mg a sustained–release formulation of melatonin was developed.

Because of its novel formulation, Circadin® releases melatonin gradually over 8-10 hours, therefore mimicking the body's natural release of melatonin and resulting in the re-setting of natural circadian rhythms and the encouragement of natural, restorative sleep.[4]

CIRCADIN EFFICACY®

The efficacy of Circadin® was established in 3 pivotal studies:

NEURIM I was a Phase II, double-blind, placebo–controlled, parallel–group, sleep laboratory (polysomnographic; PSG) study. It investigated the efficacy of Circadin® tablets versus placebo in inducing and maintaining sleep in outpatients aged 55 years or over, who were suffering from primary insomnia.[5]

Following a 2-week run-in period of single-blind placebo treatment, patients were randomised to receive either Circadin® tablets or placebo for a double-blind period of 3 weeks, before ending the study with a 3-week withdrawal period.[5]

The results showed that Circadin®:

- significantly shortened sleep-onset latency by 7 minutes, compared with 1 minute as seen in the placebo group (p=0.0111)[5]
- decreased the duration of wake prior to sleep onset (DWAPSO) by 50%[5]
- significantly improved quality of sleep (QOS) at the end of the treatment period, compared with baseline values (p=0.004, LSEQ questionnaire)

Deteriorations in daytime functioning, such as those seen with the use of benzodiazepines (BZDs), did not occur with Circadin®. On the contrary, a significant improvement of daytime psychomotor skills and arousal was observed after treatment with Circadin®.[5]

Circadin® had a clear pharmacological effect, compared with placebo, producing significant effects on sleep induction. Furthermore, after stopping the active treatment, sleep parameters returned close to baseline values, indicating that Circadin® does not cause rebound effects. Additionally, Circadin® did not adversely affect daytime functioning (as is seen with the use of BZDs), but may instead be associated with an improvement in daytime psychomotor skills.[5]

Subsequent Circadin® clinical studies used a new therapeutic principle in insomnia therapy. They were designed to evaluate the effect of Circadin® on subjective parameters such as quality of sleep and daytime functioning, as these endpoints are essential to patients' feeling of well-being.

Lemoine et al. investigated the effects of three weeks Circadin® versus placebo treatment in a multi–centre randomised placebo-controlled study involving 170 primary insomnia outpatients aged ≥55 years.[6] Improvements in quality of sleep (QOS) the night before and morning alertness (Behaviour Following Wakening, BFW) were assessed

- Circadin® significantly improved quality of sleep (-22.5 versus -16.5mm, p = 0.047), quality of night (0.89 versus 0.46 units, p = 0.003) and morning alertness (-15.7 versus -6.8mm, p = 0.002) compared with placebo[6]
- The improvement in quality of sleep with Circadin® was significantly correlated with the improvement in morning alertness, suggesting a beneficial treatment effect on the restorative value of sleep[6]
- 47% of patients receiving Circadin® had a concomitant improvement in quality of sleep and morning alertness compared with 27% of patients receiving placebo[6]
- Patients did not show any emerging symptoms during the run–out period, suggesting a lack of withdrawal effects[6]

Lundbeck Circadin®

Circadin® Clinical Data

Wade et al. carried out a study involving 354 primary care patients in the UK.[7] It consisted of a 2-week, single blind, placebo run-in period followed by a 3-week double blind treatment period with Circadin® or placebo, one tablet per day, two hours before bedtime. The primary end point was predefined as a responder analysis. A responder was defined as a patient who improved by at least 10mm on both the QOS and BFW scales of the LSEQ.[7]

- Results demonstrate a significant advantage of Circadin® over placebo (26% of responders in the Circadin® group vs. 15% in the placebo group; p = 0.014)[7]
- A significant and clinically relevant shortening of time period from "lights out" to beginning of sleep (sleep latency), to the same extent as most frequently used sleep medications was also found (-24.3 vs. -12.9 minutes; p = 0.028)[7]
- 70% of patients who responded to Circadin® (demonstrated concomitant improvements in quality of sleep and morning alertness) also experienced a clinically relevant improvement in quality of life compared to only 24% in non-responders (See Fig 1)[7]

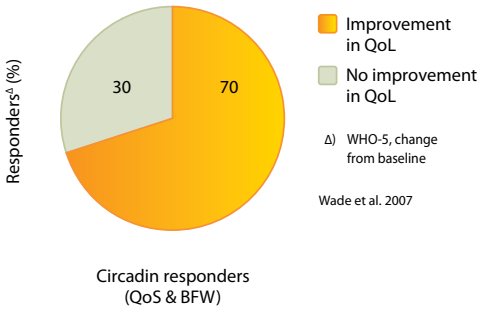

Fig 1: 70% experienced an improvement in Quality of Life

Circadin® has demonstrated a consistent improvement in sleep across the three pivotal studies, illustrated in Fig 2.

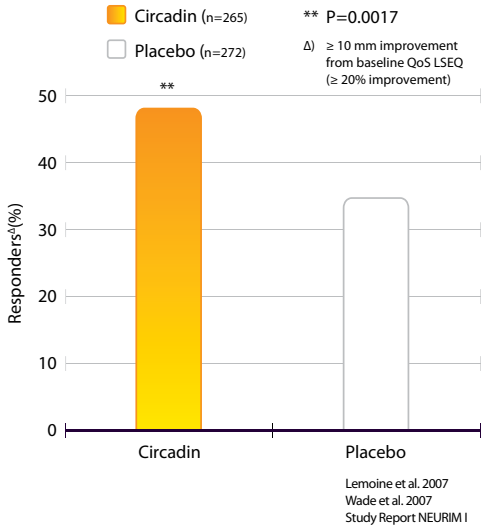

Fig 2: Consistent improvement in QoS across studies

SAFETY & TOLERABILITY

There is no evidence from clinical data on melatonin to suggest concern over the long-term use of Circadin®. Circadin® has been used open-label for up to 12 months. The overall incidence of adverse events throughout the development program with Circadin® was low and even less than with placebo. [7] Some of the adverse effects reported include headache, sore throat, back pain and weakness.

Abrupt withdrawal of some benzodiazepine hypnotics is associated with rebound insomnia; a return of insomnia worse than prior to treatment. There is no evidence of rebound insomnia with the use of Circadin® at recommended doses.[6, 8]

Unlike zolpidem, Circadin® is not associated with impairment of memory recall or driving skills at any time after dosing, as illustrated in Fig 3. [8]

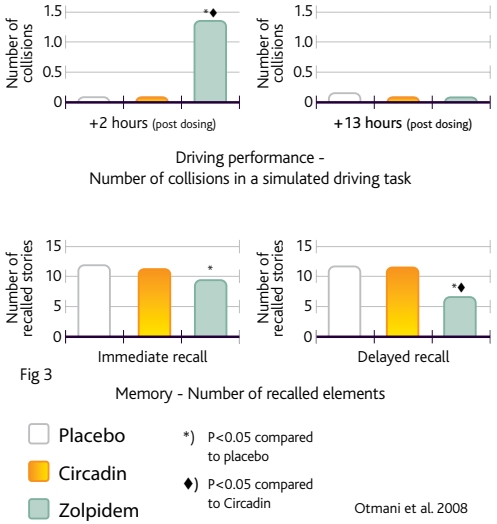

Fig 3

However, as Circadin® may cause drowsiness, caution is recommended when driving.

DRUG INTERACTION

There are no contraindications to concomitant administration of other drugs. However, Circadin® may enhance the sedative properties of benzodiazepines and non–benzodiazepine hypnotics, such as zalepon, zolpidem and zopiclone. Also, caution is advised in patients on fluvoxamine, 5- or 8-methoxypsoralen, cimetidine, and oestrogens due to pharmacokinetic interactions which increase melatonin levels. [4] In addition, quinolones may give rise to increased melatonin exposure and carbamazepine and rifampicin may give rise to reduced plasma concentrations of melatonin.

Circadin® has not been studied in pregnant women, and is not recommended during pregnancy or lactation.

No safety concerns have been raised with concomitant use of other commonly used medications such as antihypertensives, antidiabetics and lipid-lowering drugs.

DOSAGE AND ADMINISTRATION

Circadin® is indicated as monotherapy for the short–term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 years and over. The recommended dose is 2mg once daily, 1-2 hours before bedtime and after food. This dose should be continued for three weeks for optimal effect.[4]

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