PRESS RELEASE

Novel treatment offers insomnia sufferers hope of quality sleep

Circadin® improves quality of sleep and morning alertness

Copenhagen, Denmark – 13 May 2008: A new, first in class sleep medication is launched today, offering hope for thousands of sufferers of insomnia in Europe. Circadin®, sustained-release melatonin, provides natural sleep by increasing the body's own level of this naturally occurring hormone throughout the night.[1]

Melatonin is the hormone responsible for regulating the circadian rhythm (or sleep cycle) and enabling restorative sleep. Circadin®, the first melatonin agent approved by the European Medicines Agency (EMEA), is now available for the treatment of primary insomnia.[1] Circadin® is the first approved sleep treatment to work by ensuring melatonin coverage all through the night. Unlike existing sleep medications, it is not associated with problems such as dependency and poor next day functioning.[1,2]

What is insomnia?
It is estimated that primary insomnia affects 1-10% of the general population, increasing to up to 25% in the elderly.[3]

Surveys have shown that insomnia can have a negative impact on many areas of patients' lives, including health, relationships, family life and work life. Sleep deprivation is associated with psychological disorders, including depression, decreased immune function and cardiovascular disease. [4,5,6,7,8]

Dr Alan Wade, medical director of CPS Research, Glasgow, Scotland said: "The launch of Circadin® marks a huge advance for people that suffer from insomnia. It's the first treatment that can work in a natural way to establish restorative sleep with no hangover effects the next day. Improvement in quality of life and next day functioning are the goals in treating insomnia, and Circadin® delivers on both of these endpoints."

A new treatment paradigm
Traditionally insomnia has been diagnosed on the basis of *quantity* of sleep – i.e. how long it takes to get to sleep or how long a person sleeps for. While it is important not to ignore quantity of sleep, this is a matter of individual need. What matters to all patients, regardless of the amount of sleep they need, is *quality* of sleep. It is the quality of sleep which results in morning alertness, improved functioning the following day and better quality of life. Circadin® is the first sleep drug with proven efficacy on all these parameters. [9]

What is melatonin?
Melatonin is a naturally occurring hormone that regulates the circadian rhythm in humans and animals. It is the signal of night and day, and of sleep and awake time.[10] Circadian

rhythm is often referred to as the 'body clock'. In the evening, the retina of the eye responds to the fading light and signals a small gland in the brain called the pineal gland to release melatonin. Melatonin levels peak in the middle of the night, and then slowly decline until morning, ensuring restorative sleep throughout the night.[11]

As a person ages, the night-time production of melatonin tends to decrease, and the levels of melatonin in elderly people with insomnia are lower than in healthy persons. As the prevalence of insomnia increases with age, it appears that insomnia in elderly people may be caused by this reduced melatonin secretion, as opposed to simply age alone.[11, 12, 13, 14, 15] Circadin® mimics this pattern of melatonin release throughout the night to promote restorative sleep with no evidence of impairment on next day functioning.[1]

Efficacy of Circadin® in clinical trials

Circadin® has proved to be an effective treatment in clinical studies for over 55s with primary insomnia.[16]

The trials showed that almost half of patients taking Circadin® experienced a significant improvement in quality of sleep, and nearly 40% improved on morning alertness, as measured by the Leeds Sleep Evaluation Questionnaire.[16]

This is important in the treatment of insomnia because improvements in sleep quality, rather than quantity, translate into greater improvements to next day functioning and quality of life.[9] In fact 70% of patients responding to Circadin® on both quality of sleep and morning alertness reported a significant improvement in quality of life as measured by the WHO-5 well-being scale.[3]

Other study endpoints included sleep latency (or time to get to sleep), and a clinically significant reduction in time was found in the Circadin® group, similar to that of traditional sleep medications.[3]

Circadin® mode of action avoids side effects associated with traditional sleep treatments[3]

Current sleep treatments have been associated with adverse reactions such as daytime sedation (or 'hangover'), impaired memory, driving skills and concentration. Furthermore, abrupt withdrawal of benzodiazepine hypnotics is associated with a return of insomnia worse than before (rebound insomnia), and they are also known to carry a risk of dependency. [13,5]

Clinical studies with Circadin® have not shown any risk of rebound insomnia nor any impairment on memory or psychomotor functioning at any point after dosing.[1]

Circadin® has a positive safety profile and in clinical studies the incidence of adverse events with Circadin® was low and even less than with placebo.[2] Adverse effects were generally mild and infrequent and those reported included headache, sore throat, back pain and generalised feelings of weakness.[1]

June Fraser, a former insomnia sufferer who was involved in the Circadin® clinical trials said, “Insomnia was a huge burden on my family, home and work life, but traditional therapies often made me feel worse than missing a night’s sleep. Circadin® helped me to get back into a natural sleep rhythm and have refreshing sleep. Being able to get up in the morning, feeling refreshed, feels like a weight has been lifted from my shoulders.”

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Notes to editors

About insomnia

Insomnia is the most common sleep disorder and is characterised by difficulty falling asleep or difficulty in maintaining sleep resulting in poor next day functioning.[4] It is estimated that between 30 and 45% percent of the world’s population suffers from insomnia.[4] The condition can present as primary or secondary insomnia. Secondary insomnia occurs when a physical or mental condition or problem causes an inability to sleep (for example pain, anxiety); primary insomnia is where no other reason for the condition is identified. The prevalence of primary insomnia increases with age and affects up to 25 percent of the elderly population.[4] The increase in prevalence is associated with the decrease in melatonin that occurs with age.

About Circadin®

Circadin® was approved via the central procedure of the European Commission on 29th June 2007, and indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over. Circadin® is the approved trade name in the whole EU. Lundbeck holds commercialisation rights to Spain, Germany, UK, Italy, France, Ireland, Portugal, Poland, Hungary, Romania, Czech Republic, Slovak Republic, Slovenia, Bulgaria, Cyprus, Malta and Liechtenstein, representing 75% of the market potential in Europe. Lundbeck also holds exclusive rights to commercialise Circadin® in Asia, Latin America and other major markets such as Australia and Turkey. Following regulatory filing and approval Lundbeck expects to market Circadin® in the first markets outside of Europe in 2009.

Nycomed holds the commercialisation rights to the remaining markets in Europe. At the end of February 2008, Circadin® had been launched by Nycomed in Austria, Belgium, Denmark, Estonia, Finland, Greece, Iceland, Latvia, Lithuania, and Norway.

About Lundbeck

H. Lundbeck A/S is an international pharmaceutical company engaged in the research and development, production, marketing and sale of drugs for the treatment of psychiatric and neurological disorders. In 2006, the company's revenue was DKK 9.2 billion (approximately EUR 1.2 billion or USD 1.6 billion). The number of employees is approximately 5,300 globally. For further information, please visit www.lundbeck.com.

References

1. Circadin®, Summary of Product Characteristics http://www.emea.europa.eu/humandocs/PDFs/EPAR/Circadin®/H-695-en6.pdf, last accessed 16 April 2008.
2. Tyrer P, Murphy S, Riley P. The benzodiazepine withdrawal symptom questionnaire. J Affect Disord 1990; 19: 53–61.
3. Wade *et al.* Prolonged-release melatonin for the treatment of insomnia: Targeting quality of sleep and morning alertness. *Ageing Health* 2008; 4(1): 11-21
4. Léger D, Poursain B, Neubauer D *et al.* An international survey of sleeping problems in the general population. *Curr Med Res Opin* 2008; 24(1): 307-317
5. Taylor DJ, Lichstein KL, Durrence HH. Insomnia as a health risk factor. *Behav Sleep Med* 2003; 1: 227-247
6. Ohayon MM, Zulley J. Correlates of global sleep dissatisfaction in the German population. *Sleep* 2001; 24: 780-787
7. Okuji Y, Matsuura M, Kawasaki N *et al.* Prevalence of insomnia in various psychiatric diagnostic categories. *Psychiatry Clin Neurosci* 2002; 56: 239-240
8. Katz DA, McHorney CA. Clinical correlates of insomnia in patients with chronic illness. *Arch Intern Med* 1998; 158: 1099-107
9. Wade *et al.* Efficacy of prolonged release melatonin in insomnia patients ages 55-80 years: quality of sleep and next day alertness. *Curr Med Opin* 2007:23(10); 2597-2605
10. Zisapel *et al.* Sleep and sleep disturbances; biological basis and clinical implications. *Cell Mol Life Sci* 2007; 64: 1174-1186
11. Lewey *et al.* Light suppresses melatonin secretions in humans. *Science* 1980; 210(4775): 1267-1269
12. Haimov I, Laudon M, Zisapel N *et al.* Sleep disorders and melatonin rhythms in elderly people. *BMJ* 1994; 309(6948): 167
13. Waldhauser F, Weiszenbacher G, Tatzer E et al. Alterations in nocturnal serum melatonin levels in humans with growth and aging. J Clin Endocrinol Metab 1988; 66(3): 648-652
14. Zeitzer JM, Daniels JE, Duffy JF et al. Do plasma melatonin concentrations decline with age? Am J Med 1999; 107(5): 432-436
15. Corman B, Léger D. Sleep disorders in elderly. Rev Prat 2004; 54(12): 1281-1285
16. Lemoine et al. Prolonged release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 and older and has no withdrawal effects. J Sleep Res 2007; 16: 372-380