Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Melatonin

Proprietary Product Name: Circadin

Sponsor: Commercial Eyes Pty Ltd

December 2009

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Product Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of decision	28 November 2009
Active ingredient(s):	Melatonin
Product Name(s):	Circadin
Sponsor's Name and Address	Commercial Eyes Suite 6 651 Victoria Street Abbotsford Vic 3061
Dose form(s):	Modified release tablet
Strength(s):	2 mg
Container(s):	Blister pack (PVC/PVDC/Al)
Pack size(s):	21 tablets
Therapeutic use:	Monotherapy for the short term treatment (up to 3 weeks) of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over.
Route(s) of administration:	Oral
Dosage:	One tablet (2 mg) per day

Product Background

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, a hormone produced by the pineal gland, regulates circadian sleep cycles. 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.

Current 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. Melatonin is available via the Special Access Scheme.

Synthetic melatonin is proposed for use in persons over 55 years of age who suffer from insomnia. It is intended to be taken 1-2 hours before bedtime, after food.

Regulatory Status at the Time of Submission

Circadin was approved for marketing in the EU in June 2007. The approved indication is *monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.* An initial application to the EMEA was withdrawn after objections were raised. The subsequent successful application to the EMEA contained 6 additional studies all of which were contained in the data package submitted to the TGA. It is also approved in Croatia, Israel and Chile with similar indications.

An application was withdrawn in Canada after an appeal was rejected. Health Canada transferred regulatory control of melatonin to the Natural Health Products Directorate (NHPD) in 2003. The current submission is not the same as the submission made to Health Canada.

Circadin was rejected in Switzerland in 2003 due, according to the sponsor, non-acceptance of the clinical relevance of the therapeutic treatment. This decision was based on a different data set than the current submission and further data were not accepted by the Swiss regulatory agency within the original submission. Further review of the additional data was then examined and Swissmedic issued a pre-decision non-approval letter and the file was withdrawn. The application was re-submitted on 27 June 2008. Pre-approval was received on 11 June 2009, with approval consequential upon favourable assessment of response to questions by the authority.

No submission has been made in the USA. Melatonin has been available over-the-counter in the USA since 1993.

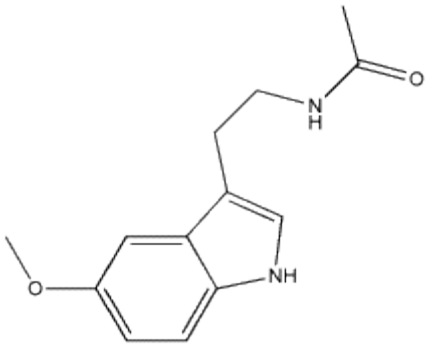
Product Information

The approved product information current at the time this AusPAR was developed is contained at attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

The drug substance has the following structure:



It is synthesised by acetylation of 5-methoxytryptamine with acetic anhydride and contains no asymmetric centres. It is a slightly off-white odourless crystalline powder that does not appear to exhibit polymorphism. It is very slightly soluble in water (0.01%) and dilute hydrochloric acid (0.08%). It is manufactured at either of two sites but the particle size is controlled at only one of those sites. This is acceptable as the drug substance is dissolved in methanol during manufacture of the tablets. Two reactants have specifications and are commercially available. The same applies for standard solvents. A standard reaction schema is used with adequate controls and TLC monitoring to ensure adequate acetylation has occurred. There are no intermediates. Data shows reliable manufacture and consistent assay, purity and particle size within specification. No impurities have been detected in 5 production scale batches at over 0.1%. Those procedures that are not pharmacopoeial monographs were adequately described. HPLC is used for assay and related substances with acceptable results. In-house reference standards are satisfactory.

Despite its relatively low aqueous solubility, melatonin is classified as highly soluble in accordance with the Biopharmaceutics Classification System due to the low tablet strength. It is completely absorbed when administered orally, although its absolute bioavailability is only 15% due to an 85% first pass effect. Hence, the drug is classified as BCS Class 1.

The drug substance is to be stored in fibreboard or HDPE drums with polyethylene food grade 500 gauge liners. The stability of the drug substance has been investigated and the results are satisfactory.

Drug Product

Circadin tablets are plain, uncoated, unscored tablets. Their prolonged release properties are conferred by the presence of an excipient. Conventional excipients have been used in formulation. No incompatibility issues have arisen although no formal studies have been done during development. Standard development occurred for the tablet formulation. Circardin tablets exhibit excellent stability hence container type is less important, however standard opaque, moisture resistant PVC/PVDC blister packs sealed with 20 micron Al foil are used. The pack Al foil 250/40 polymer film is a PVDC coated rigid PVC film and consists of polyvinyl chloride homopolymer vinyl chloride vinyl acetate copolymer and methylmethacrylate-vinylidene chloride copolymer. The blister foil is Al foil gauge 20/1000 hard tamper bright side heat sealed lacquered and dull side protective lacquered. This is food grade and complies with USA/EU requirements. Manufacture occurs at two sites. All excipients comply with Ph Eur except for methanol which complies with the German Pharmacopoeia. Specification of methanol supplied from Merck indicates compliance with PhEur, BP and NF. There are no novel excipients. Lactose complies with current EU TSE requirements and is sourced from cow's milk suitable for human consumption. Magnesium stearate is of vegetable origin. All non pharmacopoeial tests were well described. Two satisfactory standard procedures were used. No impurities/degradants were detected in any batch at release. Stability data were satisfactory and support a shelf life stored under 25 ^{o}C for 60 months when stored protected from light.

A level A *in vitro-in vivo* correlation (IVIVC) has been claimed using this dissolution method. However, the assay method used in the bioavailability study in which the IVIVC was established has been deemed unreliable. The absence of a validly established IVIVC does not, in itself, render the application unapprovable, but any future changes to the formulation or method of manufacture would require increased scrutiny.

The *in vitro* dissolution rate of the tablets increases significantly in the presence of ethanol. It is likely that dose dumping would occur *in vivo* if the tablets were taken with alcohol. There is a warning in the CMI not to drink alcohol before or after taking Circadin tablets.

Biopharmaceutics

Endogenous plasma levels of melatonin (about 10 pg/mL during the day, 30 pg/mL at night) are very low compared to the levels obtained after administration of one Circadin tablet (C_{max} about 1200 pg/mL).

One bioavailability study (Study 22940) was evaluated in detail. It was a single dose, crossover study, which showed, ostensibly, that food has no significant effect on the AUC of the tablet, but decreases C_{max} by about 13%. No dose dumping was evident in individual subjects. As expected, the tablet gave a significantly lower C_{max} than an oral solution of melatonin, but the AUC of the tablet was about 20% higher than that of the oral solution. A steady state study was not performed because levels of melatonin return to endogenous levels between doses.

The results of Study 22940 should be discounted because of significant problems with the method used to assay melatonin in plasma (a commercial RIA kit). Quality control samples analysed throughout the course of the study gave assay results in the range 59-76% of the expected results. The company claims that this is not of concern because, despite the observed inaccuracy, the precision of the method was found to be satisfactory. In the absence of a satisfactory explanation for the poor accuracy of the assay method, this argument cannot be accepted.

It is noted that the tablet formulation proposed for registration was used in all pivotal clinical studies.

Quality Summary and Conclusions

The Pharmaceutical Subcommittee reviewed this application at its 125th meeting. The PSC endorsed the questions raised by the TGA and recommended that the PI include information on the solubility and pKa of the drug substance. Information on the pKa was subsequently included. The PSC also recommended that the *Pharmacokinetics* section of the PI be amended to reflect the results obtained in the studies submitted with the application. The company has provided justifications for the figures included in the PI, and those justifications have been referred to the Clinical Delegate.

Prior to consideration by ADEC, this application was referred back to the PSC for information and comment on the deficiencies in the assay method used in Study 22940 (see Conclusion, page 36). In the evaluator's opinion, the results of Study 22940 should be discounted, and ADEC should consider whether the application is approvable in the absence of this study.

III. Non-Clinical Findings

Introduction

The nonclinical submission for melatonin consisted of both company and literature data. Company data consisted of two primary pharmacology studies, a protein binding study, a cytochrome P450 induction/inhibition study, a repeat-dose toxicity study each in rats and dogs, a combined repeat-dose toxicity and carcinogenicity study in rats, genotoxicity studies *in vitro* and *in vivo* and reproductive toxicity studies in rats and rabbits. Toxicokinetic data were limited for animal toxicology studies.

Literature references covered some aspects of melatonin pharmacology, pharmacokinetics and toxicity. However, the literature search strategy was not provided, nor was any rationale provided for inclusion or exclusion of data from the literature publications, which at times were not all inclusive.

Primary and safety pharmacology studies and the pharmacokinetic profiling of melatonin in some species were limited. However, there were generally sufficient data to overcome these and other relatively minor deficiencies.

Toxicology studies were sufficiently comprehensive, GLP-compliant, in an appropriate number and type of species (where demonstrable), for sufficient duration, with adequate numbers, dose levels (based on BSA or AUC), and appropriate administration routes for the investigation of a new chemical entity potentially employed for long term oral human use.

Overall, the nonclinical studies provided for melatonin have sufficiently characterised the pharmacological and potential toxicological profile of this endogenous compound.

Pharmacology

Primary pharmacodynamics

Primary pharmacology studies characterised melatonin binding sites/receptors, production and release mechanisms, sleep inductive and circadian effects.

Sleep induction

There is no simple animal model for investigating the sleep modulating effects of melatonin, since it induces changes that are typical for the dark period of each species.

Nonetheless, a literature study in monkeys has shown promotion of sleep onset at endogenous melatonin levels prior to dark onset. In pigtail macaques given daily oral melatonin for one week, 2 h before lights out, a minimum effective dose of melatonin promoting sleep onset compared with placebo of 5 µg/kg was established. This dose produced mean circulating plasma melatonin levels of 54 pg/mL, which was within the range of normal endogenous peak levels for this species. While no information about the pharmacokinetic profile of melatonin in this species was provided to validate its use as a surrogate human model, this study suggests that physiological melatonin levels induced by exogenous melatonin facilitate sleep induction in a similarly diurnal species.

Sedative hypnotic activity of melatonin was also demonstrated by the potentiation of barbiturate-induced sleep in rodents in both literature and company based studies with doses ranging from 0.05-40 mg/kg IP. Average ED_{50} values for the duration of the loss of righting reflex also ranged from 6-110 mg/kg IP, PO or IV in mice and rats. These values were within a similar magnitude of the doses employed in the rat toxicity studies (0.3-200 mg/kg PO), suggesting pharmacologically active doses were employed in these studies.

Additional limited literature data also suggested a direct sedative effect of melatonin in 4 day old chicks (2.5 mg; jugular vein or IP) and cats (25-30 µg; injected, not specified).

Functional melatonin receptors

The physiological effects of melatonin are mediated by pharmacologically specific melatonin receptors located in the brain and periphery.

In mammals, two high-affinity melatonin receptors (MT1 and MT2) of the G-protein coupled receptor family have been cloned, and a third melatonin receptor/binding site, MT3, with distinct pharmacological properties, has also been described. The MT1 and MT2 receptors expressed in mammals, including humans, have a very narrow distribution in the brain. The MT1 receptor is mostly expressed in the suprachiasmatic nuclei (SCN); the MT2 receptor is distributed in the SCN and other areas of the CNS as well as in the periphery.

While MT1 receptors have been detected in various brain regions in animals and humans, their functional role in regions outside the SCN has not been determined. It has been suggested that at the SCN, melatonin has two distinct actions on the circadian clock mediated by MT1 and MT2 receptors: the MT1 receptors are thought to inhibit neuronal firing while the MT2 receptors are implicated in the phase-shifting response. According to the sponsor, no physiological activities have yet been ascribed to the MT3 sites.

Mechanism of action

The mechanisms underlying melatonin's sleep facilitating action are not entirely clear and no relevant data have been provided. The sponsor has suggested several hypothetical mechanisms including lowering of core body temperature via a direct effect on

thermoregulatory mechanisms, interactions with GABA-A receptors, modifying the release of monoamine neurotransmitters involved in sleep or arousal, inhibiting the release of glutamate and acute suppression of SCN activity by MT1 receptors. However, these mechanisms have not been investigated in any great detail in the current submission.

However, what is known is that in animals and humans, the regulation of endogenous pineal melatonin appears to involve a complex interplay of responses to both light (via the hypothalamic oscillator in the SCN) and day-length. Light has two effects on pineal melatonin, with the light-dark cycle synchronising the circadian pacemaker, while acute light exposure at night rapidly reduces serotonin N-acetyl transferase (SNAT) activity, thus inhibiting melatonin production. Studies have shown that exogenous melatonin can shift the endogenous melatonin cycle, thereby resetting the SCN activity rhythm.

Melatonin has been implicated in entraining circadian rhythms *in vivo* in several animal species, including humans, with timing of dosing during the endogenous melatonin cycle often considered critical for this action. Studies have also shown that melatonin is produced from other sources outside the pineal gland (including the retina, harderian gland and GI tract), which may explain the persistence of some circadian effects of light even after pinealectomy in some species.

In animals and humans, studies have also shown that nocturnal increases in pineal melatonin production are dependent on the environmental lighting cycle, regardless of whether a species is normally nocturnally or diurnally active. Because day-length changes throughout the year, there are also seasonal effects on melatonin rhythm. In many species, longer melatonin pulses have been observed in winter or in association with longer dark periods. This phasing and duration of melatonin production in response to photoperiod has been shown to act as a temporal signal to reproductive, thermoregulatory and behavioural systems.

Secondary pharmacodynamics and safety pharmacology

Secondary and safety pharmacology studies of melatonin were limited to literature references provided by the sponsor. Secondary pharmacology studies provided focussed on melatonin's general protective role in experimental animals, including support of the immune and endocrine systems, anti-oxidant/free-radical scavenging activities, anti-tumour and anti-ageing effects and amelioration of a wide range of metabolic or physiological disorders. However, these studies are of limited direct pharmacological relevance or clinical value for the current application and were not evaluated.

In contrast, melatonin has been implicated in several central and peripheral effects including changes in CNS, neuroendocrine and cardiovascular functions, which are directly relevant to its safety assessment (discussed below). No specific studies were provided on potential respiratory or renal effects, while those examining potential GI effects were limited to protection studies only. These are considered minor deficiencies for this application, given the chronic toxicity studies performed in rats and dogs.

Central nervous system effects

Melatonin induced a range of dose-related CNS effects in rodents. Lower doses of melatonin ($\leq$ 20-40 mg/kg IP) induced sedative/hypnotic effects, while higher doses ($\geq$ 20 -200 mg/kg IP) elicited anxiolytic, analgesic, anticonvulsant and motor effects, indicative of a therapeutic window between potential sleep inductive and other (undesirable) CNS effects. Available ED_{50} values for reducing motor activity were 210 mg/kg IP and 450 mg/kg PO and for prevention of tonic extension seizures were 115 and 159 mg/kg IP for two respective challenge media in mice.

Similarly, literature data on the acute toxicity of melatonin reported CNS effects at high (400 mg/kg; route not specified) melatonin doses including piloerection, ptosis, a marked lack of motor activity and ataxia. CNS effects including salivation, forelimb paddling, rooting in cage bedding and facial tremors were also evident at the high doses (50-200 mg/kg PO) employed in the rat repeat-dose and reproductive toxicity studies. Based on BSA dose comparisons, exposure at this dose range was > 200-900x that expected at the proposed clinical dose, for these mild (with the exception of facial tremors in 2 animals at 200 mg/kg/day PO in one study) CNS effects.

Cardiovascular and respiratory effects

Melatonin receptors have been reported on the anterior cerebral and caudal arteries of rats and on the coronary and pulmonary arteries of pigs. Dissociation constants determined for the rat arterial receptors have suggested tight binding (70-267 pM) and potential physiological relevance of these receptors. Additionally, *in vitro* studies in both isolated ovine artery and vein demonstrated the potential for melatonin to relax vascular smooth muscle.

Administration of IV melatonin (0.3-0.4 mg/kg) to baboons produced no effect on left ventricular end-diastolic and end-systolic volumes, stroke volume, ECG or blood pressure up to 1 h post-dose. However, cardiac output and ventricular ejection fraction were significantly increased which, coupled with bradycardia, suggested a positive inotropic action. In contrast, melatonin (10^{-4} M) lacked inotropic and chronotropic actions in isolated guinea pig and rat heart. However, in rats IV melatonin (30-60 mg/kg) produced a dose-related fall in mean arterial pressure, heart rate and serotonin release. In contrast, another study noted that 10 mg/kg melatonin (route not specified) did not alter blood pressure in cats or alter contractile force or ECG in dogs, although the data were limited. An additional study in rats has suggested that SC melatonin (1-10 mg/kg) may exert a protective effect on heart sarcolemmal membrane function.

Literature data on the acute toxicity of melatonin have reported cardiovascular effects at high (400 mg/kg; route not specified) melatonin doses in rodents including vasodilation and muscle relaxation, with even higher doses associated with laboured respiration.

The conflicting reports of melatonin's effects on cardiovascular function are likely related to the varied test systems (*in vitro* vs *in vivo*), species, administration routes and doses employed, confounding interpretation of these results.

Nonetheless, in a 6 month repeat-dose toxicity study in dogs, doses up to 8 mg/kg/day PO had no remarkable effect on blood pressure or heart rate at 15-20 min post-dose when examined at weeks 13 and 25. Melatonin exposure at the highest dose in this study (8 mg/kg/day) was > 120x that expected at the proposed clinical dose. Cardiovascular evaluations were not performed in rat repeat-dose toxicity studies. While no effects on respiration have been reported in chronic toxicity studies of melatonin in rats and dogs, no specific respiratory assessments were performed in these studies.

Gastrointestinal effects

No specific studies investigating potential GI effects of melatonin have been provided. While no remarkable GI effects were reported in chronic toxicity studies of melatonin in rats and dogs, no specific assessments of GI function were made in these studies. It is noted that gastroprotective effects of melatonin have been reported in rats (30 mg/kg IP) and pigs (5 mg/kg in food).

Endocrine effects

Melatonin affects hormones controlling sexual function in many species. There is some evidence suggesting that melatonin may be inhibitory to pubertal development, with the timing of exposure reported as critical for activity in some studies. Melatonin has also been implicated in the control the reproductive cycle and oestrus cycling in several species. According to the sponsor, the use of melatonin SC implants in the control of oestrous cycle is well-established and a licensed product has been registered in Australia and overseas for many years under the trade names of Regulin and Prime-X.

Melatonin administered by SC implant (18-36 mg), injection or orally with food has been used to stimulate ovarian activity and advance breeding season in domestic livestock (sheep, goats and deer). Melatonin implants (0.78-78.2 mg SC) have also been used to induce early priming in minks.

In young female mice, 0.2 mg/day SC melatonin reduced mammary tissue development following dosing for 2-7 weeks onwards. In young female rats, 4 mg/L melatonin in water (≈100 µg/day) for 30 days reduced ovarian and uterine weights and serum oestradiol concentrations. In pregnant rats, 2.5 mg/kg SC melatonin altered LH and prolactin and/or FSH levels in 5-55 day old offspring. In adult female rats, 12.8 mg/kg IV melatonin increased serum prolactin, 10 mg/L in water for 7 days altered ovulation, and 100 µg SC for 24 h was shown to re-establish ovulation in acyclic animals. In middle-aged female rats, 0.4 mg/L melatonin in water (≈10 µg/night) for 45 weeks delayed age-related changes in serum LH levels and oestrus cycling.

In pubertal or young male rats, 5-100 µg/day SC, 50 µg/day IP or 4 mg/L melatonin in water (≈40 µg/day) reduced testosterone secretion and gonadal (seminal vesicle, prostate and/or epididymis or testicular) weight following dosing for 3-8 weeks. Plasma LH and FSH levels and pituitary GnRH receptor numbers were also reduced in rats given 5-100 µg SC melatonin for 3-4 weeks. In a separate study in young male rats, 100 µg/day SC melatonin for 1.5-16 weeks delayed pubertal development. In adult but not pubertal male rats, 180 µg/kg SC melatonin for 4 days caused significantly increased prostate weight. Age-dependent effects on prostatic androgen receptors were also observed. Melatonin (100 µg SC) administration to juvenile male rats for 20 days significantly decreased testicular, epididymal, seminal vesicle and ventral prostate organo-somatic indices. Abnormal progression of spermatogenesis and decreased ability of the Leydig cells to produce testosterone both *in vivo* and *in vitro* was also observed, in association with a lower number of binding sites for hCG, diminished testosterone production and marked decrease in serum LH levels.

In young female hamsters, daily melatonin injection (10-25 µg/day) for 10 weeks disrupted oestrous cyclicity, the normal pattern of gonadotropin secretion, and resulted in atrophy of the uterus and vagina, coincident with depressed serum and pituitary prolactin and serum estradiol levels. Adult female hamsters given melatonin (10-25 µg SC) for 4-7 weeks also became acyclic and showed a diurnal pattern of LH secretion; oestrous activity resumed after 4-6 weeks post-dose. In juvenile male hamsters given melatonin (10-5000 ng SC over 12 h) for 4-12 days and adult male hamsters given melatonin (10-25 µg SC) for 4-10 weeks in several studies, reproductive (particularly testicular) and/or accessory organ weights were reduced. Depressed plasma and/or pituitary FSH, LH, prolactin, testosterone and/or thyroxine levels were also observed in adult hamsters following 4-10 weeks dosing in several studies.

In ewes implanted with melatonin in the hypothalamic premammilary area for 80 days (release rate >10 µg/day; after 3-5 days ≈5.5 µg/day), LH secretion was stimulated and prolactin secretion was reduced.

Chronic toxicity studies of melatonin in rats and dogs for up to 24 and 6 months, respectively, showed no remarkable and/or consistent organ weight changes, macroscopic or microscopic reproductive organ abnormalities. Limited testis staging data in rats given 150 mg/kg/day PO melatonin for 13 weeks (control and high dose rats only) in the combined toxicity/carcinogenicity study also did not reveal any spermatogenesis abnormalities. Melatonin exposure at the highest doses (8 and 150 mg/kg/day in dogs and rats, respectively) in these studies represented a 121-682x safety margin over the proposed clinical dose, based on BSA and AUC.

Nonetheless, it should be noted that the actions of high exogenous doses of melatonin on hormonal and reproductive functions may be of relevance for long-term use.

Comparative Pharmacokinetics

Company pharmacokinetic studies of melatonin were limited to rat, dog and rabbit toxicokinetic data, a protein binding study and a CYP450 induction/inhibition study. However, additional literature data regarding the ADME profile of melatonin were provided. Overall these studies suggested that exogenously administered melatonin is well-absorbed following oral administration, widely distributed and virtually completely metabolised in animals and humans, in a similar fashion.

The pharmacokinetic behaviour of melatonin was similar in test animals and humans. In all nonclinical species employed for toxicity testing (rat, dog, rabbit), melatonin was rapidly and extensively absorbed, with a T_{max} range of 10-75 min, compared with 1.5-3 h in humans. Oral bioavailability was low in humans, averaging around 15% across studies, while averaging 54% in rats and > 100% in both dogs and monkeys. However, a lower dose administered to dogs resulted in a much lower value of 17%. Thus, the pharmacokinetics in these species and in humans appear to be non-linear and likely as a result of saturable first-pass hepatic metabolism.

Systemic clearance was slightly lower in humans (0.6-1.0 L/hr/kg) compared with rats (2.11 L/hr/kg), dogs (3.84 L/hr/kg) monkeys (1.68 L/hr/kg). However, a much lower dose was administered to humans, so it is possible that the slightly higher clearance values observed in animals may be due to nonlinearity as opposed to species differences. The apparent elimination half-lives in the rat, dog and monkey were around 20-30 min, which are similar to the reported literature human value of 40-50 min.

In rats, dogs and monkeys, the steady-state volume of distribution was similar, ranging from 1.05-1.48 L/kg and indicating moderate tissue distribution. A value of 0.55 L/kg was reported for humans in the literature, suggesting reduced tissue distribution compared with animals. However, volume of distribution has been reported to vary with age, and values of 1.8-2.5 L/kg have also been reported for adult and prepubertal subjects in the literature. Thus, the high volume of distribution reported in adult subjects is consistent with findings in animals and the hydrophobicity of melatonin.

Studies in rats and hamsters indicate that melatonin is widely distributed to tissues and readily penetrates the blood-brain barrier. The highest levels of drug-related radioactivity were found in the GI and elimination organs, consistent with its passage through these tissues, while the lowest levels were detected in the brain, fat and skin. While there were no studies examining tissue distribution after repeated dosing, there is no evidence of melatonin accumulation in rats and rabbits, and only limited evidence of accumulation in dogs (toxicokinetic data). Therefore, the absence of these studies is considered acceptable.

Melatonin was also shown to cross the placental barrier to the developing fetus in rats, hamsters and monkeys, suggesting direct *in utero* exposure in these species. Milk excretion of exogenous melatonin was also demonstrated in cows, goats and rats.

Most circulating melatonin has been shown to bind to albumin in rat and human plasma at concentrations up to 1.5 mM. Melatonin was also shown to bind to human plasma proteins (albumin > $alpha_1$-acid glycoprotein > high density lipoprotein with weak binding to other proteins) over the concentration range 0.2-2 nM. Protein binding was not examined in any other species.

Melatonin is rapidly and primarily metabolised by the liver and cleared from the body. The major metabolic pathway determined in humans, mice, rats and rabbits involves 6-hydroxylation in the liver via the hepatic microsome P-450 system to yield 6-hydroxymelatonin. The second, less significant pathway is 5-demethylation to yield the melatonin precursor, N-acetyl serotonin. Both 6-hydroxymelatonin and N-acetylserotonin are ultimately conjugated to sulphate and glucuronic acid, and excreted in the urine as their corresponding 6-sulphatoxy and 6-glucoronide derivatives.

In humans, mice and rats 70-90% of urinary radioactivity was identified as the sulphate and/or glucuronide conjugates of 6-hydroxymelatonin. In rabbits, although not quantified, the sulphate and glucuronide conjugates of 6-hydroxymelatonin were also identified as major and minor metabolites, respectively. In mice, 6-hydroxymelatonin (86%) and N-acetyl serotonin (7%) accounted for 93% of total metabolites excreted. Additional minor metabolites including 5-methoxyindoleacetic acid (a compound present in the pineal gland), 1-acetyl-1,2,3,3a,8,8a-hexahydro-8a-hydroxy-5-methoxypyrrolo[2,3-b]indole (a cyclic isomer of 2-hydroxymelatonin) and 10-methoxyharmalan were identified in rat (0.06-5%) and/or human urine. Moreover, metabolomic urine analysis identified 13 melatonin metabolites in mice. However, the presence or absence of minor metabolites in species employed in toxicity testing is likely to remain unresolved given the likely differences in urinary analysis methods employed. Importantly, no melatonin metabolic profiling data were provided for dogs.

In addition to hepatic metabolism, a metabolic route in the brain has also been suggested. N^{γ}-acetyl-5-methoxykynurenamine was identified as the major melatonin metabolite in the rat brain, while N^{γ}-acetyl-N^{2}-formyl-5-methoxykynurenamine (which was degraded to N^{γ}-acetyl-5-methoxykynurenamine by the action of formamidase) was identified as a major melatonin metabolite in the rabbit brain. Interestingly, these metabolites were also detected in mouse urine, suggesting this pathway may also be present in the liver, although not fully elucidated yet.

In vitro metabolism studies suggest that 6-hydroxylation of melatonin is mediated primarily, but not exclusively, by the CYP1A family (particularly CYP1A2), while CYP2C19 appears to be a major isozyme involved in the O-demethylation of melatonin. There is also some evidence to suggest the involvement CYP2C9, and an additional isozyme previously not investigated, CYP1B1, in the metabolism of melatonin, however this has not been fully elucidated. Further *in vitro* CYP450 studies demonstrated that melatonin was able to inhibit CYP1A2 and induce CYP3A at supra-therapeutic concentrations. Thus, the potential for interactions with drugs that are substrates, inducers or inhibitors of any of these isozymes exists. While no dedicated *in vivo* enzyme induction/inhibition, pharmacokinetic interaction or toxicity interaction studies were performed, it is noted that clinical studies have been done.

Melatonin is rapidly metabolised and eliminated, with 90% of administered radioactivity excreted within 24 h of dosing in both rats and humans. Little (0-2%) unchanged melatonin was detected in rat, dog and human 24-48 h urinary samples suggesting almost complete metabolism in these species.

Toxicology

A relatively comprehensive dossier of toxicology studies was submitted, including company studies documenting repeat dose toxicity in rats (3 months) and dogs (6 months), a combined toxicity/carcinogenicity study in rats (3-24 months), genotoxicity *in vitro* and *in vivo* and reproductive toxicity in rats and rabbits, and literature data regarding single dose toxicity in the rat, mouse and hamster. Additional, albeit limited studies examining aspects of repeat-dose toxicity, carcinogenicity and reproductive toxicity in mice and rats and genotoxicity of melatonin and its metabolite 6-hydroxymelatonin *in vitro* were also provided.

All pivotal company toxicology studies complied with GLP, with melatonin administered orally (by gavage), consistent with the proposed clinical route of administration. With the exception of dogs, all species examined demonstrated exposure to both melatonin and its major metabolites following exogenous melatonin administration in pharmacokinetic studies, and are therefore considered appropriate models for toxicity testing. Since no metabolic profiling was performed in dogs, the extent of exposure to melatonin metabolites is unknown and therefore the validity of this nonclinical model cannot be confirmed. While this is considered a nonclinical deficiency, this endogenous compound is anticipated to undergo a similar metabolic pathway in dogs given its comparable pharmacokinetic behaviour in other species concurrently examined (humans, rats, monkeys), with high systemic melatonin exposure achieved in this species, suggesting a large (up to > 600x based on AUC) exposure margin for the parent compound over that anticipated clinically.

The duration of the pivotal toxicity studies (6-24 months) was adequate to support long-term use in humans and employed appropriate animal numbers (10-50/sex/group in rats and 4/sex/group in dogs, 19-20/group in rabbits (reproductive toxicity)). Dose-selection, although not always clearly justified, was based on achieving exposures "significantly higher than that targeted for use in humans for sleep" and/or "minimal toxic effects" at the highest doses. However, the absence of any severe dose-limiting toxicity or dosing feasibility constraints in rats, dogs and rabbits suggests that higher doses could have been employed in these studies. Nonetheless, high doses employed in the pivotal toxicity studies were adequate based on toxicity (minimal toxic effects at high dose) and/or pharmacokinetic endpoints, where applicable (³ 25x ratio of animal/human plasma AUC). Large inter-subject variability was evident in toxicokinetic data obtained for all species, including humans, however, this is unlikely to significantly diminish the large clinical exposure multiples determined in these studies based on AUC.

Relative melatonin exposure

Human exposure (plasma $AUC_{0\text{-}24\ h}$) to melatonin at the proposed clinical dose (2 mg PO, once daily) was estimated as 5.6 ng.h/mL from seven single dose clinical pharmacokinetic studies. The sponsor reported that melatonin does not accumulate with repeated dosing in humans, although no repeat dose clinical kinetic data were provided to substantiate this claim. Nonetheless, large inter-study variation in human exposure was noted with average AUC values ranging from 2.3-15.8 ng.h/mL. Mean male and female exposure values (based on studies where individual gender parameters

were provided) approximated 4 ng.h/mL and 14.8 ng.h/mL, respectively suggesting up to a 3-fold gender difference. High intra-study variability was also associated with these pharmacokinetic parameters with standard deviations of up to≥100%. Further, the Neurim Pharmacokinetic Review also stated that "very large individual variations in peak plasma concentrations (at least 25 fold) following oral melatonin have been consistently documented." Thus, the derived value of 5.6 ng.h/mL is considered the best possible mean estimate of clinical exposure only and safety margins derived from this value should be considered approximate only.

Additional clinical melatonin pharmacokinetic data were received from numerous literature studies using various doses and formulations of melatonin. Dose-normalising melatonin exposure (AUC) parameters, where provided, for doses similar (2-5 mg) to those intended to be used clinically, for the tablet, capsule and solution formulations, produced an average melatonin AUC value of 4.6 ng.h/mL. This value is similar to the 5.6 ng.h/mL value determined from the company studies performed with 2-8 mg melatonin and confirms the suitability of this value for clinical exposure comparisons. Where separated into gender, a slight increase in exposure was observed in female subjects in these literature publications however, the gender difference did not appear remarkable.

Estimation of systemic melatonin exposure in rat toxicity studies was also limited. In the three-month rat repeat-dose toxicity study, only C_{min} values were determined. In the combined rat repeat dose toxicity and carcinogenicity study, only day 1 and day 7 AUC values were determined. While no gender differences were apparent in this study, a trend for reduced exposure even after 1 week of dosing was observed, suggesting week 104 values could not be reliably estimated by day 1 or day 7 values. The variability of exposure parameters in this study was also shown by $C_{60\ min}$ values determined at weeks 13-104, which showed in excess of a 20-fold variability in mean values between treatment weeks, with no apparent trend in exposure changes. No pharmacokinetic parameters were determined for any rat reproductive toxicity studies.

In the dog 6 month repeat-dose toxicity, systemic exposure ($AUC_{20\text{-}t}$) was determined throughout the study (days 1, 85 and 175), with no apparent gender differences but some evidence of accumulation with repeated dosing. Similarly, systemic exposure ($AUC_{0.167\text{-}4\ h}$) was also determined in the rabbit embryofetal development study on GD 7 and 19, although the sampling regimen was limited.

Given the limited kinetic data in the rat toxicity studies, animal/human safety margins could only be estimated by dose comparisons based on BSA (and were quite different to safety margins derived from systemic exposure data, where available). In contrast, animal/human safety margins could be reasonably determined by both systemic exposure (AUC) and BSA comparisons in dogs and rabbits and appeared relatively consistent.

Overall, melatonin exposure at the highest doses employed in rat, rabbit and dog toxicity studies was associated with large (> 100x) multiples of the anticipated clinical exposure, based on BSA. Melatonin exposure in rabbits and dogs at the highest doses employed were also associated with large (> 600x) multiples of the anticipated clinical exposure, based on AUC.

Toxicity profile

Melatonin appears to have low acute toxicity. In rodents, PO or parenteral doses > 400 mg/kg elicited predominantly CNS (including piloerection, ptosis, marked hypoactivity,

ataxia) and cardiovascular (vasodilation and muscle relaxation) clinical signs, with dose-related severity.

Melatonin was generally well-tolerated following repeat dosing in rats (up to 24 months), dogs (6 months) and rabbits (two weeks, pregnant and non-pregnant). Mild treatment-related effects were observed in rats and dogs including clinical signs (salivation, forelimb paddling, raised tail, rooting in cage bedding) and/or changes in body weight (BW) and food consumption at PO doses ranging from 50-200 mg/kg/day and at 8 mg/kg/day, respectively. Based on BSA and AUC (dogs only), these doses represented more than 100-900x the exposure anticipated at the proposed clinical dose. Clinical pathology, urinalysis, ophthalmic, and/or indirect cardiovascular measurements were generally unremarkable and inconsistent following 3 and/or 6 months dosing in both species. Chronic toxicity studies identified the liver, thyroid and kidney as potential target organs.

Hepatic effects

In the combined toxicity/carcinogenicity study in rats, liver weights were slightly increased at melatonin doses of 75 and 150 mg/kg/day in both males (10-13%) and females (8-10%) after 13 weeks dosing; this was reversible following the four week treatment-free period. To a lesser extent, the liver weight increase was also observed in males (7%) but not females at 150 mg/kg/day after 26 weeks dosing. Organ weights were not assessed after 104 weeks.

No remarkable changes in liver enzymes or macroscopic liver changes were observed at 13, 26 or 104 weeks. However, minor centrilobular hypertrophy was detected in 9/10 (compared with 0/10 control) and to a lesser magnitude, 9/19 (compared with 0/20 control) males given 150 mg/kg/day melatonin after 13 and 26 weeks of dosing, respectively. Liver hypertrophy was not observed in any treated females or male recovery animals, indicating reversibility, and no microscopic liver changes were observed after 104 weeks dosing in either gender.

In the repeat dose toxicity study in dogs, liver weights were slightly increased at melatonin doses of 8 mg/kg/day in males (11%) and dose-independently in 1.5 and 8 mg/kg/day in females (7-16%) after 6 months dosing. No remarkable macroscopic liver changes were observed, while chronic liver inflammation was observed in 4/8 dogs from all dose groups given 0.4-8 mg/kg/day melatonin compared with 1/8 control dogs (for both genders combined). While no clear treatment-relationship was established in this species, this was possibly confounded by the small subject numbers and hence greater intra-group variability in parameters examined, and the greater duration of exposure.

These findings suggest that the liver may be an organ of histopathological adaptive change, with a reduced activity at this organ with repeated dosing potentially linked to the induction of enzymes. Overall, the No Adverse Effect Level (NOAEL) for the reversible liver changes in rats was 15 mg/kg/day, suggesting a 68x safety margin over the proposed clinical dose, based on BSA. A NOAEL for possible liver changes in dogs could not be clearly established.

Thyroid effects

In the combined toxicity/carcinogenicity study in rats, treatment with melatonin for 26 weeks was associated with dark thyroid at doses of 75 (3/20 males, 1/20 females) and 150 (9/19 males, 7/20 females) mg/kg/day, correlated with agonal congestion/haemorrhage microscopically; these thyroid findings were not observed in control animals. Increased dark and/or large thyroid was also observed in rats treated for 104 weeks at doses of 75 and 150 mg/kg/day. Microscopically, treatment-related increases in both incidence (refer below) and severity of thyroid pigment and thyroid follicular cell hypertrophy were also evident at doses of 75 and 150 mg/kg/day compared with control animals.

A slightly increased incidence of thyroid follicular cell tumours was also evident in male but not female rats given 150 mg/kg/day melatonin for 104 weeks (7/50 = 14% compared with 3/50 = 6% in both control groups; refer to *Carcinogenicity*).

In the repeat dose study in dogs, thyroid weights were slightly increased at melatonin doses of 8 mg/kg/day in males (8%) and dose-independently at all doses (0.4-8 mg/kg/day) in females (5-19%) after 6 months dosing, without remarkable macroscopic or microscopic thyroid changes.

Overall, the thyroid was identified as a potential organ of long-term physiologic or metabolic adaptive change, in test species. The NOAEL for non-neoplastic thyroid changes in rats was determined as 15 mg/kg/day, suggesting a 68x safety margin over the proposed clinical dose, based on BSA.

Renal effects

In the combined toxicity/carcinogenicity study in rats, kidney weights were marginally increased at melatonin doses of 75 and 150 mg/kg/day in males (5-7%) and 150 mg/kg/day in females (7%) after 13 weeks dosing, a reversible effect following four treatment-free weeks. A marginal kidney weight increase was also observed in males (7%) only at 150 mg/kg/day after 26 weeks dosing. Organ weights were not assessed after 104 weeks.

Macroscopic renal findings were limited to kidney pelvic dilatation in 2 female rats given 150 mg/kg/day melatonin for 13 weeks. Microscopically, a treatment-related increase in renal pigment incidence (refer below) and a marginal increase in the severity of chronic nephropathy was observed in rats given 150 mg/kg/day melatonin for 104 weeks.

Overall, the kidney was identified as a potential organ of long-term physiologic or metabolic adaptive change, at least in rats. Although the clinical implications of these findings are uncertain, the NOAEL for potential renal effects, even at 15 mg/kg/day, suggests a considerable (68x) safety margin over the proposed clinical dose, based on BSA.

Genotoxicity

Melatonin was tested for potential genotoxic effects in an adequate GLP-compliant battery of *in vitro* (bacterial reverse mutation, forward gene mutation, chromosomal damage) and *in vivo* (mouse micronucleus) assays, all conducted with appropriate doses/concentrations. Two additional literature studies examined the genotoxic potential of melatonin and/or a major metabolite, 6-hydroxymelatonin in bacterial cells *in vitro*.

Melatonin was neither mutagenic in bacterial or mammalian cells *in vitro* nor clastogenic in human lymphocytes *in vitro* or mouse erythrocytes *in vivo*. Some minor deficiencies in company study methodology were identified, including omission of a tester strain to detect A-T point mutations and the TA98 strain in the Ames test and exclusion of some concentrations in the chromosomal aberration assay *in vitro*, but these are not considered to affect study conclusions. The melatonin metabolite 6-hydroxymelatonin was also not mutagenic in bacterial cells *in vitro* at appropriate concentrations, although a limited number of tester strains (TA 97, TA 98, TA 100 only) were employed, limiting the validity of this assay. The overall test profile indicates that melatonin is not genotoxic under the conditions of proposed clinical use.

Carcinogenicity

Carcinogenicity studies are generally required for any pharmaceutical where the clinical use is anticipated to be > 6 months (ICH guideline 3BS8a). While the recommended dose for

Circadin is continued daily dosing for three weeks, no maximum treatment duration is recommended. As outlined in ICH guideline S1B, one long-term rodent carcinogenicity study and one either short or medium-term *in vivo* rodent test system (including models of initiation-promotion in rodents or models or carcinogenesis using transgenic or neonatal rodents) or long-term carcinogenicity study in a second rodent species are recommended for carcinogenicity testing.

The carcinogenic potential of melatonin was assessed in a GLP-compliant combined toxicity/carcinogenicity study in rats, an appropriate species for human toxicity testing. This study employed adequate animal numbers, doses, the proposed clinical administration route and was conducted for sufficient duration. While two short-medium term carcinogenicity studies in mice and/or rats conducted by the National Institute of Environmental Health Sciences (US-NTP) were provided (in summary form), the relative value of these studies was compromised by experimental deficiencies identified in each (discussed below). However, it should be noted that carcinogenicity studies are not generally needed for endogenous substances given essentially as replacement therapy (i.e., physiological levels) (ICH 3BS8a). Thus, the absence of a second, adequately designed and conducted study examining the carcinogenic potential of melatonin is considered only a minor deficiency in the context of the application.

In the "short"-term study conducted by the US-NTP, the effect of melatonin administration (50-200 mg/kg PO (gavage)) on mammary tumourigenesis in transgenic female mice with the c-neu breast cancer oncogene was examined. However, the ability of melatonin itself to induce neoplasms in any organs or tissues was not investigated in this study, and animal numbers (6/group) and treatment duration (6 months) were limited. Parameters examined were confined to BW, food consumption, survival and effects on mammary tumour growth and development. BWs were significantly lower in the melatonin groups given 100-200 mg/kg/day, with mortality considerably higher in the melatonin group given 200 mg/kg/day (8/16 survivors compared with 12/16 controls). Melatonin delayed the appearance of palpable tumours and inhibited the growth of mammary tumours dose-dependently. However, it should be noted that the reduced survival in the 200 mg/kg group may have influenced tumour development if younger animals were included in this evaluation.

In the "medium"-term study conducted by the US-NTP, the carcinogenicity of L-tryptophan, a melatonin precursor, was examined in rats and mice administered dietary concentrations up to 5000 ppm for 78 weeks, on a 5 out of 7 days/week regimen. Fundamentally, the administration of L-tryptophan, not melatonin, limits the relevance of this study. While there is literature evidence to suggest that the administration of L-tryptophan increases plasma melatonin levels in chicks and rats, this was not confirmed in this study and exposure to melatonin is unknown. In addition, the unconventional dosing regimen, reduced dosing period (1.5 years), the low animal numbers (15-35/group) employed, the significant age of the study (suggesting GLP non-compliance), the limited parameters reported (survival, BW, microscopic findings), and the presentation of summary data only, severely compromises the validity of this study. Nonetheless, BWs were notably reduced in both male rats and male and female mice at both treated doses compared with respective controls in this study. However, survival did not appear affected in either species or gender. The incidence of some neoplastic and non-neoplastic findings appeared slightly elevated, but these changes were predominantly confined to a single gender and/or species. The incidence of any particular neoplasm for either species did not reach statistical significance (at $p<0.05$). Therefore, according to the sponsor, L-tryptophan was not carcinogenic in these assays. However, no historical control data were provided nor other toxicity parameters assessed to determine the significance of these findings. Therefore, the relevance of these findings is unclear.

In the pivotal company toxicity/carcinogenicity study in rats, a slight, significantly (p=0.036) increased incidence of pituitary adenomas was observed in males given 150 mg/kg/day melatonin (15/49 = 31%) compared with controls (8/50 = 16%; control1) or (10/49 = 20%; control2) for 2 years, but not females. It is noted that 4/15 pituitary adenomas in the 150 mg/kg/day group were fatal, compared with 0/8 and 1/10 for the control groups, respectively. However, the report points out that the "FDA guidelines for common tumours, such as pituitary adenomas, propose that only pairwise comparisons at the 0.01 level are of statistical note". Thus, significance of these adenomas is below the value triggering concern. Moreover, limited available historical control data (CRL, 2003) for pituitary adenomas (range 21.8-50.9%; mean 31.9%) in male Wistar rats suggest this value is within reasonable agreement of expected tumour incidence for this rat strain.

A slight, but insignificant (p=0.088) increase in the incidence of thyroid follicular cell tumours was also observed in males given 150 mg/kg/day melatonin (7/50 = 14%) compared with controls (3/50 = 6%), again not in females. Historical control data (CRL, 2003) for thyroid follicular cell adenomas (range 1.7-12.7%; mean 5.8%) suggest this tumour incidence, while not statistically significant, is slightly elevated beyond typical tumour incidence for this rat strain.

Concerns were also raised by the Committee for Medicinal Products for Human Use (CHMP)of the European Medicines Agency regarding the thyroid tumours in high doses in male rats and a mechanistic explanation was requested.

Liver enzyme induction was suggested as the possible mechanism of action. In their response, the sponsor noted that "increases in thyroid follicular cell hypertrophy are common responses in rats to exposure to a number of xenobiotics particularly those which induce hepatic microsomal enzymes" and that it "is apparent from the 13 week and 26 week toxicity data that changes occurred in the livers of male rats exposed to high doses of melatonin (75 or 150 mg/kg/day) were consistent with hepatic microsomal enzyme induction. Hepatic microsomal enzyme induction, is known to change the metabolism of hormones including thyroxine most likely accelerate the metabolic elimination of thyroxine. This decline in thyroxine may have been compensated for by release of increased levels of thyroid stimulating hormone (TSH) from the anterior pituitary. Increased TSH levels can produce a variety of changes in the thyroid follicular cell including induction of hyperplasia and hypertrophy."

In a further response, the sponsor also noted that "the individual animal listings of liver and thyroid changes from animals in the carcinogenicity study have been reviewed and there are no obvious correlations between liver pathology and neoplastic thyroid pathology. This is not particularly surprising given the data from the 13 week and 26 week studies, which indicated that the liver hypertrophy which was clearly present after 13 weeks of treatment was less prevalent after 26 weeks of treatment. These data suggest that an adaptive change was taking place in the livers with continued melatonin exposure. It remains very probable that the hepatic microsomal enzyme induction which was postulated did, in fact, occur and may well have been of sufficient extent and duration to accelerate the metabolic elimination of thyroxine, precipitate TSH release and subsequently thyroid follicular cell hyperplasia, hypertrophy and ultimately result in a slight increase in thyroid follicular cell neoplasia in males. It should, perhaps, be reiterated that the increase in thyroid follicular cell neoplasia following exposure in the carcinogenicity study to high doses of melatonin (150 mg/kg/day) was not statistically significant. No published data have been identified which indicate how long microsomal enzyme induction needs to persist in order to potentiate thyroid follicular cell neoplasia, but it seems probable that such an event occurring during the period of rapid

growth, which would have been in progress during the first 13 weeks of exposure at least, would have been very likely to have a biological effect."

Following these responses, the CHMP commented that "the mechanism for increased thyroid tumours in rodents remains partially unsolved as data in favour of a correlation between liver enzyme induction, pituitary (TSH) and thyroid hormone changes and thyroid tumours is lacking." The sponsor was therefore requested to revisit the available data in the repeated dose studies and, if available, the levels of thyroid hormones and TSH in these animals. The sponsor committed to provide these data in post-authorisation as a follow-up measure.

In the current application, a study examining plasma levels of TSH, Total T3 (T3) and Total T4 (T4) in available blood samples from the combined 3, 6 and 24 month toxicity study was provided. Plasma were analysed for TSH, T3 and T4 in the day 1, week 13, 78 and 104 samples for the control, 15, 75 and 150 mg/kg groups. Overall, there appeared to be no remarkable difference in TSH, T3 and T4 levels in animals dosed with up to 150 mg/kg/day compared with control values at the various sampling time points.

However, the sponsor noted an almost 2x increase in mean TSH levels for day 91 (week 13; 2243 pg/mL) compared with day 1 (1132 pg/mL) values for the three male rats sampled at the 150 mg/kg dose. According to the sponsor, these males also had "minimal centrilobular hypertrophy with minimal to slight inflammatory cell foci". They further stated that "the available TSH data, although limited in terms of animal numbers, clearly supports the mechanism of action: liver enzyme induction leading to accelerated metabolic elimination of thyroxine and consequent TSH release." However, "no result" was available for female rat TSH levels at day 1 and 91 for comparison. Moreover, there was no increase in T3 or T4 values at any dose, nor were any consistent increases in TSH at the lower (15 and 75 mg/kg) doses observed between day 1 and 91.

Plasma TSH, T3 and T4 levels at weeks 78 and 104 indicated no clear dose-trends nor correlation with the associated thyroid or liver pathology in individual animals. However, the sponsor considered the absence of a dose-related trend in plasma TSH levels as supportive evidence for the "mechanism of action proposed that adaptive change in the liver following prolonged exposure to melatonin occurred." They further stated that "it would be expected that the accelerated metabolism of thyroxine would have reduced or ceased by week 78 and the stimulus to potentiate TSH release would have similarly declined." However, week 78 and 104 TSH levels were also elevated (2-6x) in 150 mg/kg males.

Overall, data from this study do not suggest any consistent effect of melatonin on the thyroid hormone levels. However, some information has been provided that suggests that, at least in males given 150 mg/kg/day melatonin, there may be at least a weak correlation between liver enzyme induction and TSH levels. Levels of absolute T3, free T4 and TSH were determined in clinical study NEU BP in which 38 patients were given 2 mg/day Circadin for four weeks. In this study, these hormone levels did not significantly differ between the treated and placebo groups. Thus, the clinical data provide some reassurance that the effects observed in the rat, if mediated by the proposed mechanism, are of limited clinical concern at the proposed dose.

Overall, the slightly elevated incidence of pituitary adenomas and thyroid follicular cell adenomas observed in male rats given 150 mg/kg/day PO melatonin for 2 years, would appear to be of limited clinical concern, given their increase in a single gender only, common occurrence at levels within available historical control data (pituitary adenomas) or lack of statistical significance and plausible mechanism of action (thyroid adenomas). Given the tumour incidence was only examined in the high dose (150 mg/kg/day) and control groups, a

NOAEL could not be clearly established. Nonetheless, this dose represented a 700x margin over the proposed clinical dose, based on BSA.

Reproductive toxicity

A comprehensive reproductive toxicology assessment of melatonin was conducted in rats and rabbits, an appropriate species for human toxicity testing. All company studies were conducted according to GLP, utilising adequate animal numbers and appropriate high doses, although toxicokinetic data were provided for rabbits only. Literature data were provided regarding placental transfer and milk excretion in several species, and limited reproductive toxicity assessments in mice, rats and *in vitro*.

Reproductive studies with melatonin illustrated slight maternotoxicity (clinical signs and mild reductions in BW and food consumption) in rats at oral doses ranging between 50-200 mg/kg/day during all stages of the reproductive cycle. The NOAEL for maternotoxicity in these studies (10-200 mg/kg/day) represented a 45-900x safety margin over the proposed clinical dose, based on BSA.

Increased pre-implantation loss (15% compared with 7.5% in controls) was observed in litters from rats given 200 mg/kg/day PO melatonin prior to mating and during early embryonic development. However, this increase was not statistically significant and values only just exceeded the historical control range (8.7-14.5%). Moreover, other aspects of reproductive performance, for both genders, and early embryonic development were not affected by treatment. Therefore, NOAEL for fetal effects was established at the highest dose in this study (200 mg/kg/day), representing a 900x safety margin over the proposed clinical dose, based on BSA.

Similarly, no remarkable effects on embryofetal growth, viability or morphological development were observed in rats at melatonin doses of up to 200 mg/kg/day PO during the embryofetal development period. Thus, the NOAEL for fetal effects was also established at the highest dose in this study (200 mg/kg/day), representing a 900x safety margin over the proposed clinical dose, based on BSA.

However, combined embryofetal and peri- and postnatal treatment of rats with doses of 200 mg/kg/day oral melatonin was associated with reduced growth and viability of the offspring during lactation and some slight physical developmental delays in male offspring. The NOAEL for pup effects (based on the slight growth impairment and developmental delays) in this study was 55 mg/kg/day, representing a 250x safety margin over the proposed clinical dose, based on BSA.

No maternotoxicity or remarkable effects on embryofetal growth or viability were observed in rabbits given oral doses of melatonin up to 150 mg/kg/day during the embryofetal development period. However, the incidence of fetal malformations of the head, joint and spine appeared slightly increased with treatment at 150 mg/kg/day (1.9% compared with 0% control) and outside of available historical control data ($\leq$0.8 -1.2%). Nonetheless, it was noted that these increases were due to incidences in a single litter, suggesting a potential congenital rather than a dose-related origin. In contrast, a range of visceral (absence of a lung, abnormal eye texture, discoloured thymus) and skeletal (incomplete ossification, alignment shift, long or fused) variations were slightly, and in some cases, significantly increased with treatment at 150 mg/kg/day. Interpretation of some of these findings was confounded by the high control incidences for some variations, isolation of the specified variation to a single or limited number of centra, sternebrae, ribs or vertebrae *etc* and absence of historical control data. In any event, the fetal NOAEL (based on visceral/skeletal

variations) in this study was 50 mg/kg/day, representing a 700x safety margin over the proposed clinical dose, based on AUC.

No placental, fetal or milk levels of melatonin were analysed in any reproductive toxicology studies. However, other animal studies (rats, hamsters, goats, monkeys, cows) indicate maternal transfer of exogenous melatonin to the fetus via the placenta and/or milk.

Additional (limited) reproductive studies of melatonin in mice reported no embryofetal effect of a single 40 mg/kg SC dose administered on GD 8.5 or two SC doses of 120 mg/kg administered on GD 7.5 and 8.5 when examined on GD 10.5 and 17.5, respectively. However, this is not unexpected given the limited fetal exposure during embryogenesis. *In vitro* studies using cultured GD 8.5 mouse embryos showed that 100-200 µg/mL melatonin increased the number of abnormal mouse embryos, however the clinical significance of this finding is unknown. Reproductive studies of melatonin in rats were somewhat at odds. In one study, administration of 2.5 mg/kg SC during "pregnancy" produced no remarkable effect on weight gain, litter size, gender composition or pregnancy duration. In contrast, administration of 2.5 mg/kg SC from GD 0 through to parturition in a second study marginally (≤10%) reduced ovarian and pineal gland weights, significantly reduced pituitary gland weight, delayed vaginal opening and lowered LH levels in the offspring. Overall, based on the limited data provided, poor study design and/or study inconsistencies, these additional literature-based studies have very limited value-adding effect on reproductive toxicity assessments of melatonin.

Paediatric Use

There are no adequately conducted nonclinical studies in young animals to support the use of melatonin in children, and treatment of paediatric patients is not proposed.

Local tolerance

No local tolerance studies of melatonin were conducted, but this is considered unimportant given the proposed oral route and absence of local irritative effects in chronically-treated rats and dogs.

Non-Clinical Summary and Conclusions

The findings in the relatively comprehensive nonclinical dossier do not raise any major concerns for the registration of melatonin as proposed by the sponsor.

Primary pharmacology studies of melatonin provided some, albeit limited, evidence of promotion of sleep onset in monkeys and sedative hypnotic activity in rodents.

The pharmacokinetic profile of melatonin was relatively well-characterised with similar metabolic transformation pathways demonstrated in species used for toxicity studies (with the exception of dogs) and humans. Melatonin metabolism was shown to be mediated by the hepatic enzymes CYP1A1, CYP1A2 and CYP2C19, and melatonin was able to inhibit CYP1A2 and induce CYP3A.

Toxicology studies were adequately conducted and sufficiently comprehensive to characterise melatonin's safety profile, although toxicokinetic sampling was limited. The liver, thyroid and kidney were identified as target organs for toxicity at high (68x) no-effect exposure margins over those anticipated clinically.

The incidence of pituitary adenomas and thyroid follicular cell adenomas was increased in males in the rat carcinogenicity study. Although a no-effect dose was not established, the dose where tumorigenic responses occurred was *ca* 700x the clinical dose, based on BSA.

The genotoxicity profile of melatonin was negative. The data suggest the carcinogenic liability of melatonin in humans is low.

Reproductive toxicity effects were limited to slight maternotoxicity in rats, increased incidences of growth impairment and developmental delays in rat pups, and increased incidences of visceral and skeletal malformations/variations in rabbit fetuses at high (45-900x) no-effect exposure margins over those anticipated clinically.

There are no nonclinical objections to the registration of melatonin.

IV. Clinical Findings

Introduction

The clinical submission for Circadin included 6 exploratory studies, 7 special population studies, 2 dose-finding studies (one of which featured up to a 12-month extension phase), 1 Phase III sleep laboratory study, 2 pivotal Phase III placebo-controlled trials and 1 Phase III trial using an external comparator. Where full study reports have been provided, all were carried out in accordance with Good Clinical Practice guidelines. The pivotal trials featured adequate but not large numbers of patients for their designs (the largest featuring less than 170 per arm), while the exploratory and special population studies included tens of patients only.

Efficacy endpoints are a difficult issue in studies of treatments for disorders of sleep. A number of tools exist to attempt to quantify various parameters of sleep, and several were used in the studies submitted in the application. Indeed, no two of the Phase III trials submitted used the same efficacy endpoint.

Pharmacokinetics

Nine studies examined the pharmacokinetics of Circadin and or its active ingredient melatonin in 92 healthy volunteers and 505 elderly insomnia patients. In the pharmacokinetic studies plasma melatonin levels were generally determined using a validated radioimmunoassay (RIA) with a minimum quantifiable level of 1.0 pg/ml for melatonin with a plasma volume of 200 ml. 6SMT excretion in urine was determined using either a validated gel plate method with a minimum quantifiable level of 2 ng/ml 6SMT per 50 ml urine or a RIA method with a sensitivity of 0.5ng/ml urine.

Dissolution and excretion studies

Clinical Report Number: 6-92 investigated the pharmacokinetic profiles of 7 formulations (regular melatonin (RM), Sr-16, Sr-19, Sr-13, Sr-6 and Sr-12) of 2 mg melatonin *in vitro* and *in vivo*. The primary objective of this study was to develop a melatonin formulation that mimicked the endogenous release of melatonin form the pineal gland and to characterise the pharmacokinetic and dissolution profiles of the candidate formulations. The release profiles of six 2 mg tablet formulations of melatonin were examined. Based on these results Sr-16 and Sr-19 were chosen for further development and were compared to RM in *in vivo* studies examining the urinary excretion of 6SMT following a 2 mg dose of each formulation. The peak excretion rates of the Sr-16 and Sr-19 formulations occurred at 4 hours post dosing compared with 1 hour post dosing for the RM formulation.

Comparative pharmacokinetics of three tablet formulations of melatonin

The pharmacokinetics of three formulations (RM, Sr-16 and Sr-19) of 2 mg melatonin were examined in a double blind cross-over study (Clinical Report No. 6-92) in 7 healthy elderly volunteers (4 female) who suffered from insomnia aged 69 to 76 years. Although both the

RM and Sr-19 formulations reached maximal 6SMT levels of secretion 2 hours following dosing, following the RM formulation excretion returned to baseline levels 4 hours after dosing, whereas the Sr-19 formulation did not decay to baseline until 8 hours following dosing. By contrast, the Sr-16 formulation displayed a slower increase in 6SMT secretion with maximal secretion at 4 hours post dose with secretion levels returning to baseline at 8 hours and although there are some differences, the excretion profile of the Sr-16 formulation most closely mimics the endogenous production of melatonin in man.

Protein and erythrocyte binding of melatonin

The protein and erythrocyte binding of melatonin was examined in Clinical Report No. 220EG71L003. The in vitro protein binding of [O-methyl-3H]melatonin was examined by equilibrium dialysis and included binding to: albumin (HAS), a-1-acide glycoprotein (AAG), G-globulin, lipoproteins (HDL, LDL, VLDL). Melatonin had very low affinity constants for both HAS and AAG. Results suggest that melatonin is not likely to displace the binding of other drugs to these proteins.

Effect of food on melatonin and Circadin pharmacokinetics

The pharmacokinetics of melatonin were examined in a three-way study in 8 healthy male subjects aged 24 to 29 years. Based on Tmax exogenous melatonin is rapidly absorbed and excreted, however, fasting subjects displayed lower Tmaxs for melatonin than fed subjects (1.6 and 2.6 hours, respectively) and times of maximal 6SMT secretion (2.8 and 4.3 hours).

A single dose, two way cross-over study (Study No. RD 625/22940) examined the comparative pharmacokinetic and food interaction following a 2 mg dose of Circadin (slow release melatonin) in 14 healthy elderly volunteers (4 female) aged 54 - 66 years. Under fasted conditions AUC_1 was similar for both formulations. Under fed conditions AUC_1 was noticeably higher for melatonin solution (5059.6 compared with Circadin 3949.4 pg.h/ml), whereas Tmax was similar for both formulations (0.5 hours).

Ascending dose study for Circadin

An open-label, balanced, non-randomised, three-period, single ascending-dose (1, 4 and 8 mg) pharmacokinetic study (Clinical Report: CR100.96.100) was conducted in 14 healthy elderly volunteers (7 female) aged 56-69 years. The duration of the study was 17 days and each subject received a single daily dose of 1 mg, 4 mg and 8 mg Circadin following a standard meal with a 6-day wash-out between treatment periods. Based on the limited data provided (7 male and 7 female subjects) there appears to be considerable difference in the pharmacokinetics (AUC and Cmax) of Circadin/melatonin in the male and female subjects and these differences possibly warrant further elucidation.

Pharmacokinetics in the target population

The urinary secretion of 6SMT (the major metabolite of melatonin) in a large sample of insomnia patients and 6SMT levels in insomnia patients after long term treatment (6 months) with 2 mg Circadin was examined in a population pharmacokinetics study (Clinical report No. 6-00). The objectives of the study were 4-fold:

- to determine the normal range of nocturnal urinary secretion of 6SMT in large group of elderly patients;
- to determine whether the nocturnal 6SMT levels of two populations of elderly patients with insomnia from two different countries of origin is compatible with the definition of normal range;

- to determine the nocturnal 6SMT levels of elderly patients with insomnia who had been treated with 2 mg Circadin for greater than or equal to 6 months is within the normal range for elderly patients ;
- to determine whether 6SMT levels of elderly patients with insomnia who had been treated for ≥ 6 months exhibit diurnal variations. These studies were conducted in 384 elderly patients aged 55 to 75 years who had been recruited for the Neurim 4 study in France.

The results were as follows:

- The reference group of elderly insomnia patients (from the Neurim 4 study) had a mean nocturnal excretion of 6SMT of 9.54 ± 7.96 mg/12 hours.

By contrast, the mean daytime excretion of 6SMT in patients in the Neurim 4 study was lower (mean excretion of 3.17 ± 4.82 mg/12 hours).

Patients who completed 6 months of daily treatment with 2mg Circadin showed significantly increased nocturnal 6-SMT excretion than those in the reference population of study Neurim 4 (t-test, p=0.009)

There was no difference in the mean nocturnal excretion of 6SMT in Dutch and Israeli insomnia patients.

Pharmacodynamics

Drug Interactions

Four studies in the PK/PD section of the evaluation materials examined the pharmacodynamic interaction of 2 mg Circadin with other drugs, the first three as secondary objectives and the last as the primary objective of the study. The first 3 studies were conducted in 39 healthy male volunteers aged 20 to 37 years, whereas the last study in this section was conducted on 16 healthy elderly volunteers with an average age of 59 years. No pharmacodynamic studies were conducted in healthy volunteers to establish dose-response or minimum effective dose. No rationale is given by the study's authors for examining the interactions between Circadin and cimetidine, imipramine and thioridazine. By contrast, the interaction between Circadin and zolpidem was examined as it was part of a European Medicines Evaluation Agency requirement to examine a comparative reference hypnotic.

Cimetidine

A three-way, single dose cross-over trial (Study No. RD 625/22963) was conducted to examine the drug interaction between melatonin and cimetidine in healthy male volunteers aged 20 -29 years, 13 subjects completed all three phases of the study. A secondary objective of the study was to assess the effect of co-administered melatonin and cimetidine on the mood and vigilance of subjects. When compared to co-administration of 800 mg cimetidine + placebo, 2 mg Circadin + placebo and 2mg Circadin + 800 mg cimetidine significantly decreased alertness and significantly increased feebleness and lethargy 3 hours following drug administration. There was no significant difference in mood and alertness between the 2 mg Circadin + placebo group and the 2 mg Circadin + 800 mg cimetidine group suggesting that there was no pharmacodynamic interaction between cimetidine and Circadin.

Imipramine

The drug interaction between melatonin and imipramine (a tricyclic antidepressant) was examined in a three-way, single dose cross-over trial **(**Study No. RD 625/22964) in healthy male volunteers aged 22 - 33 years. A secondary objective of the study was to assess the effect of co-administered melatonin and imipramine on the mood and vigilance of subjects. Although Circadin

increased drowsiness and dreaminess in subjects 3 hours after drug administration these increases were smaller than when imipramine was given alone or in combination with Circadin. The combined drug also induced a stronger feeling of incompetence than either Circadin or imipramine alone. Imipramine alone also generated a greater feeling of trouble than either Circadin alone or in combination with imipramine, these last two results possibly suggesting that there may be a pharmacodynamic interaction between the two drugs. For the remaining 14 parameters there was no evidence of a pharmacodynamic interaction between Circadin and imipramine.

Thioridazine

A randomised, double-blind, single dose three-way cross-over study (Study No. RD 625/22965) examined the interaction between melatonin and thioridazine (an anti-psychotic) in 12 healthy volunteers aged 24 to 37. The objective of the study was to assess the effect of co-administered melatonin and thioridazine on the mood and vigilance of subjects. Co-administration of Circadin and thioridazine induced larger and longer effects on mood and alertness, particularly in the induction of a significantly stronger feeling of muzziness, than either Circadin or thioridazine when given with placebo, possibly suggesting a pharmacodynamic interaction between the two drugs.

Zolpidem

The effects of co-administration of Circadin and zolpidem (a short-term treatment for insomnia that acts on $GABA_A$ receptors), on vigilance, psychomotor functions, driving performance and blood levels were examined in a phase I, double-blind, placebo controlled, cross-over randomized monocentric study (Protocol No. NEU112001) in 16 elderly healthy male and female volunteers (12 male) mean age 59 ± 3.2 years. The primary objective of the study was to assess the effects of Circadin 2 mg on psychomotor tasks in comparison with placebo and Zolpidem 10 mg and the secondary objectives were to assess the effects of Circadin 2 mg on driving performance and wake EEG during a driving test in comparison with placebo and Zolpidem 10 mg; this study also evaluated the interaction between Circadin 2mg and Zolpidem 10mg on psychomotor tasks, on driving performance, on wake-EEG during a driving test and on blood concentrations of the two drugs.

In conclusion, zolpidem alone but not Circadin alone impaired cognitive function up to 4 hours post dosing and these impairments induced by zolpidem resolved by 12.5 hours post dosing. Co-administration of zolpidem and Circadin impaired cognitive function up to 4 hours post dosing and in many cases the impairment at 1 hour post dosing was greater than that seen when zolpidem was administered alone. These results suggest that zolpidem and Circadin interact and potentiate the negative cognitive effects of zolpidem seen at 1 hour post dosing. Without data describing the long term effects of co-administration of zolpidem and Circadin, combined use of these drugs should possibly be contra-indicated.

Efficacy

The Circadin clinical evaluation programme included trials in four broad groups reflecting the drug's stages of development.

The first group comprises six early exploratory studies, namely Study 1, Study 2, Study 3, Study 4, Study 5 and NEU30424. These generally featured small enrolments and brief treatment periods, and were designed to provide some experience on which to base later methodologies as well as early evidence for efficacy based on the presumed dose necessary to achieve melatonin concentrations present in the brain in healthy young individuals at night.

The second group comprises seven studies of Circadin efficacy in special populations (NEU201005, NEUBP, NEU951003, NEU951004, NEU961009, NEU951005 and NEU951005a). A later phase III trial, Neurim VIII, was discontinued prematurely due to recruitment problems and is included in this group for convenience.

The third group includes the two dose-finding studies Neurim IV and Neurim V and efficacy data from the long-term extension study Neurim V. For convenience it also includes the Phase III sleep laboratory study, Neurim I, which although included in this group may be considered pivotal to the submission.

The fourth group comprises the phase III trials, Neurim VII and Neurim IX. The external-control study Neurim VIIIa is also included in this group for convenience and is considered pivotal, since it was designed to address concerns raised during the application to market Circadin submitted to overseas regulatory authorities.

The submitted efficacy studies use a range of efficacy endpoint measures.

A common objective measure used in the submitted studies were parameters derived from the Somnitor™ device, an FDA-approved electronic recorder which was developed by Neurim, the US sponsor for development of the drug subject to this evaluation. The Somnitor™ is an ambulatory device worn on the wrist of the patient, which translates movements into electronic signals which are logged and later analysed mathematically ("actigraphy"). It expresses sleep quality in terms of a number of derived parameters, including sleep efficiency (the length of sleep time divided by the time in bed), wake after sleep onset (mid-sleep arousal time after the onset of sleep) and sleep latency (the period between going to bed and the onset of sleep). While formal sleep laboratory polysomnography (PSG) remains the gold standard of objective sleep quantification, actigraphy in general [(24)] and the Somnitor™ device in particular has been validated as a reasonable proxy.

The Pittsburgh Sleep Quality Index (PSQI) was developed initially as a screening tool for insomnia, and was specifically intended for use in an older adult population. It measures seven self-reported parameters (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction) as recalled by the patient over the previous month. Numerous studies have since confirmed the tool's validity and reliability, although it remains ultimately a subjective measure of sleep.

Another popular tool is the Leeds Sleep Evaluation Questionnaire (LSEQ), comprising ten self-rating 100mm-line analogue questions concerned with aspects of sleep and early morning behaviour. The LSEQ was developed as a research tool to measure medication effects on sleep variables - at baseline, during treatment, or both comparatively. It had been previously validated in English, and subsequently in other languages. The US sponsor of Circadin, Neurim Pharmaceuticals, used data from one of its non-pivotal Phase III trials (Neurim IV) to test the validity of the LSEQ in elderly insomnia patients, and to confirm its cross-cultural validity. Neurim Pharmaceuticals also used data from its Neurim IV trial to determine the minimum clinically significant difference in VAS score of 10mm. The ten questions of the LSEQ may be considered in four progressive elements of sleep, namely the ease of getting to sleep (GTS, a mean of questions 1-3), quality of sleep (QOS, a mean of questions 4-5), the ease of waking from sleep (AFS, a mean of questions 6-7) and behaviour following waking (BFW, a mean of questions 8-10). It should be noted that, in the opinion of the evaluator, the use of *elements* of the LSEQ as primary efficacy measures has not been externally validated.

Polysomnography is a specialized field beyond the scope of this evaluation. In general terms, however, the technique involves multi-channel recording of various physiological parameters of the sleeper. It typically includes several channels devoted to the electroencephalogram (EEG), several to electromyelography (EMG – detecting various muscle movements), two to electrooculography (EOG – eye movements) and one to pulse oximetry. Scoring into the recognised "stages of sleep" is performed visually, using criteria outlined in 1968 and widely validated since. The data raised by polysomnography is usually subject to considerable computer analysis. For the purposes of the submitted studies, the data broadly produced "sleep continuity parameters" and "sleep architecture parameters". One of the recognized sleep continuity parameters, the "duration of wakenings after sleep onset" (DWASO) formed the primary outcome measure in the study Neurim I.

Neurocognitive tests are often used in psychopharmacology as tools to measure the effects of drug treatments on various domains of cognition. The Test of Everyday Attention ("TEA") has gained considerable traction as a measure of attention across a broad spectrum of neuropsychology since its publication in 1996. While it has not been widely used as a surrogate measure of wakefulness and morning performance, its other applications have been well validated. The Critical Flicker Fusion ("CFF") test has been used as another surrogate measure of global cortical activation, and has been accepted for some time as a valid outcome measure in psychopharmacology. Both of these tests were utilized as secondary outcome measures in the sleep laboratory study, Neurim I.

Early Exploratory Studies

Six studies formed the early exploratory group.

Study 1

The exploratory trial referenced as "Study 1" in the submission was a Neurim-sponsored study published as "Melatonin Replacement Therapy of Elderly Insomniacs" by Haimov *et al.* in the journal *Sleep* (1995). It was a small double-blind, placebo-controlled randomized three-way crossover trial of 2mg melatonin, either as fast-release or sustained-release Sleep initiation was improved by fast-release melatonin. Both maintenance and initiation of sleep were improved over the two-month 1mg treatment, suggesting that tolerance did not develop.

Study 2, 3 and 5

None of these three studies were included in the submission; they are therefore not evaluated here.

Study 4

The study referred to as Study 4 in the submission was a Neurim-sponsored trial published as "Effects of Low Doses of Melatonin on Late Afternoon Napping and Mood" by Terlo *et al.* in *Biological Rhythm Research* (1997). It was a small double-blind, placebo-controlled randomized trial of 10 healthy young adult male volunteers, treated with controlled-release melatonin 2mg for three weeks, followed by a withdrawal phase of one week of placebo treatment. Neither objective sleep efficiency ($p = 0.087$) nor subjective sleep efficiency ($p = 0.087$) were significantly improved in this population, although wake time after sleep onset and delayed sleep offset time were significantly improved ($p = 0.013$ and $p = 0.048$ respectively) in the treatment group compared to placebo.

Study 30424

This study was a small multi-centre, double-blind placebo-controlled randomized two-period crossover trial of 2mg controlled-release melatonin in 26 elderly patients with insomnia and

melatonin deficiency. Circadin treatment achieved statistical significance ($p = 0.03$) in the 10 patients judged to be valid by the sponsor, and the authors assert a clinically-significant improvement in sleep efficiency (3.5% improvement).

Special Population Studies

The second group comprises seven studies of Circadin efficacy in special populations (NEU 201005, NEU BP, NEU 951003, NEU 951004, NEU 961009, NEU 951005 and NEU 951005a). A later phase III trial, Neurim VIII, was discontinued prematurely due to recruitment problems and is included in this group for convenience.

NEU 201005

This was a small single-centre, open-label study of Circadin efficacy in 8 patients with end-stage renal disease already on haemodialysis for at least the past three months. Patient ages ranged from 23 to 61 years, and patients were treated with 2mg daily for three weeks. A trend to better global sleep scores was seen following treatment, but this did not achieve statistical significance ($p = 0.1$). However, subgroup analysis in patients with severe insomnia found statistically significant improvement in global sleep scores ($p = 0.03$) and sleep quality ($p = 0.01$).

NEU BP

This was a multi-centre, double-blind, randomized placebo-controlled, parallel-group trial of the efficacy of Circadin in reducing the nocturnal blood pressure of 38 adult patients already taking antihypertensive drugs for at least the past two months. These drugs could include any of ACE inhibitors, beta blockers, angiotensin receptor antagonists or diuretics, either alone or in combination. Patient ages ranged from 42-83 years, and patients were treated with 2mg daily for four weeks. Treatment with Circadin also significantly increased the circadian fall in diastolic blood pressure ($p = 0.045$). A decline in the improvement noted in the Circadin-treated group was seen on stopping treatment, although the decline did not reach baseline levels. No rebound effects were noted in either group.

NEU 951003

This study was a single-centre, randomized double-blind, parallel-group study of controlled-release melatonin versus placebo, administered at 5mg daily for six months, in patients with benign prostatic hyperplasia (BPH). The study also featured a twelve-month extension of single-blind treatment with controlled-release melatonin. 59 male patients aged between 50 and 79 years enrolled, 57 concluded the double-blind treatment period and 50 completed the twelve month extension study. No statistically significant efficacy for melatonin over placebo was shown for prostate size, urine flow rate, PSA levels or subjective symptom scores.

NEU 951004

This trial was a single-centre, randomized double-blind, crossover study of controlled-release melatonin versus placebo, administered at 2mg daily for three weeks to elderly patients suffering from insomnia and already treated with benzodiazepines (BDZ). Twenty-one (21) patients were enrolled and randomized, and all completed the study; all had been treated for at least six months with at least one BDZ-containing tablet per day, for sleep. Compared with placebo, controlled release melatonin produced statistically significant improvements in all parameters: sleep efficiency (+13.6%, $p < 0.001$), sleep latency (-59.8%, $p < 0.007$), wake time after sleep onset (-48.5%, $p < 0.001$), total sleep time (+9.4%, $p = 0.027$) and number of awakenings (-29.4%, $p = 0.004$).

NEU 961009

This was a single-centre, randomized double-blind, parallel-group study of controlled-release melatonin versus placebo, administered at 2mg daily for six weeks to adult patients suffering from insomnia and discontinuing chronic use of at least one BDZ-containing tablet per day, for sleep. Thirty-four (34) patients aged 40 to 90 years old were enrolled; all completed the initial treatment period. Sleep quality scores were significantly higher in the melatonin group compared to placebo ($p = 0.04$), although it should be noted that the questionnaire used was an unvalidated instrument. The six-month extension period revealed that 24/30 patients discontinued BDZs, and 19/24 of these maintained good sleep quality without taking BDZs.

NEU 951005

This was a single-centre, randomized double-blind, two-period crossover study of controlled-release melatonin versus placebo, administered at 2mg daily for three weeks to diabetic patients suffering from insomnia. A five-month extension of open-label treatment was available to patients who wished to continue. 38 adults aged 46 to 77 years old were enrolled and completed treatment, although non-compliances with the actigraphic recordings used in the efficacy analysis meant that efficacy data for 14 patients was missing. Statistically significant improvements were seen in three of the actigraphic parameters measured in patients treated with Circadin compared to placebo: sleep efficiency (+3.6%, $p < 0.05$), wake time after sleep onset (-38.6%, $p < 0.01$) and number of awakenings (-33.3%, $p < 0.01$).

NEU 951005a

This was a single-centre, randomized double-blind, placebo-controlled study of controlled-release melatonin versus placebo, administered at 2mg daily for six months to diabetic patients suffering from insomnia. Although 42 patients were randomized and completed the study, only 17 patients had data at baseline and at the end of treatment available for efficacy analysis. Statistically significant improvements were seen in patients treated with Circadin compared to placebo, in terms of sleep efficiency (+6.23%, $p < 0.02$) and wake time after sleep onset (-27.7min, $p < 0.02$). There were no statistically or clinically significant improvements in the neuropathy or quality of life indices between the two treatment groups.

Non-Pivotal Clinical Efficacy Studies

These included the Phase III sleep laboratory study Neurim I (1997), and the Phase IIb/III dose-ranging studies Neurim IV (1997) and Neurim V (2000).

Neurim I

This was a single-centre, randomized, double-blind parallel group, placebo-controlled sleep laboratory study to assess the effects of Circadin 2mg on the sleep-wake cycles of 40 patients aged at least 55 years, with insomnia according to DSM-IV criteria. The study's primary objective was a comparison of Circadin 2mg against placebo on the total Duration of Wakenings After Sleep Onset (DWASO), a hypnographic variable extracted by polysomnography. Although not explicitly stated in the report, the Duration of Wakenings After Sleep Onset (DWASO, the primary efficacy measure) did not demonstrate a statistically significant change with Circadin 2mg compared to placebo. Circadin demonstrated a significant change in some of the variables assessing sleep induction, when compared to placebo. Sleep onset latency was significantly decreased in the Circadin group ($p = 0.011$) compared to both placebo and pooled group baseline values. Similarly, the derived total duration of time awake prior to sleep onset was significantly decreased in the Circadin group ($p = 0.011$) compared to both placebo and the pooled baseline values. When the time awake before sleep onset is expressed as a percentage of total time asleep, there was also a significant decrease under Circadin compared to placebo ($p = 0.02$). In the case of all three of these outcomes where a significant treatment effect was shown, the respective

parameters measured returned towards baseline on withdrawal of the study drug (and in all cases initially overshot the baseline at the "early withdrawal" time point, but not to the point of statistical significance).

Neurim IV

This was a French multi-centre, double-blind, parallel-group, randomized, placebo-controlled dose-ranging study of the efficacy of Circadin in 491 primary insomniacs over the age of 55, in both responders and non-responders to a single-blind administration of Circadin 2mg. The period of the trial was from January 1997 to December 1997. The primary objective of this study was to determine the minimum dose of Circadin with a clinically useful effect in the target population. A statistically-significant improvement ($p < 0.001$) in QOS was seen during V2 (Circadin 2mg) compared to V1 (placebo). Along with QOS, statistically-significant improvements ($p < 0.001$) in the other LSEQ parameters – GTS, AFS and BFW – were seen following the V2 treatment phase (Circadin 2mg).

Neurim V

This was a multi-centre, double-blind, parallel-group, randomized placebo-controlled dose-ranging study of the efficacy and safety of Circadin in improving the sleep of adult insomniacs. It featured a six-month open-label extension phase for treatment with Circadin 2mg for long-term safety and efficacy data. An analysis of the change-from-baseline in QOS revealed no statistically significant improvement for any treatment group, in either the intention-to-treat (ITT) population or the per-protocol (PP) population. Indeed, the only statistically significant improvement ($p = 0.026$) that could be derived in change-from-baseline in QOS was a post-hoc subgroup analysis controlling for patient age (over 55 years) in the Circadin 2mg treatment group. The other parameters from the LSEQ followed the QOS in its lack of significance during the double-blind period, regardless of treatment group.

Pivotal Studies

Three trials were submitted as pivotal to the proposed indication. Neurim VII and Neurim IX were studies of efficacy of the proposed dose of Circadin 2mg for the treatment of insomnia in elderly patients. Neurim VIIIa was an external comparator study, performed to validate the methodology of earlier studies with the use of Zolpidem 10mg as an active comparator.

Neurim VII

This was a multi-centre, randomized double-blind, placebo-controlled parallel group study of the effect of Circadin 2mg on sleep quality and behaviour during the day in patients aged at least 55 with insomnia according to DSM-IV criteria. A total of 47 sites in France and Israel were involved, and the period of study was from January 2001 to March 2001. A planned enrolment of 166 was hoped to allow at least 77 patients to complete three weeks of double-blind treatment in each arm. The primary efficacy measure was the change in QOS (in mm) under treatment with Circadin compared to placebo (Table 1). At baseline, the mean QOS was roughly equivalent in the two groups (65.09 for placebo, 65.46 for Circadin). The mean change at week three was -16.87 ± 17.79 for the placebo-treated group, but -23.11 ± 20.77 for the Circadin-treated group. The treatment difference in the PP population was -6.24 (95% CI of -12.24 to -0.23). Analysis-of-variance confirms this as a statistically significant difference ($p = 0.042$). Analysis using the ITT population also found statistical significance ($p = 0.047$).

Table 1 - QOS (in mm) and change in QOS, PP population (Neurim VII)

Visit	Placebo	Circadin® 2 mg
Patients in PP population	86	76
Baseline (end of 2-week run-in):		
N	86	76
Mean ± SD	65.09 ± 11.991	65.83 ± 12.627
Range	44.0 – 94.7	40.8 – 93.7
End of 3-week double-blind period:		
N	86	75
Mean Change ± SD	-16.87 ± 17.786	-23.11 ± 20.772
Range	-65.0 – 23.8	-69.7 – 7.7
End of 2-week run-out period		
N	84	73
Mean Change ± SD	-20.06 ± 20.196	-16.54 ± 21.533
Range	-65.7 – 26.0	-84.3 – 25.5

The "Getting to Sleep" (GTS) parameter was derived from the mean of the first three questions in the LSEQ. An improvement from baseline was seen in both treatment groups and in both the PP and ITT populations, but this did not achieve statistical significance (p = 0.892 for the PP population) (Table 2).

Table 2 - GTS (in mm) and change in GTS, PP population (Neurim VII)

Visit	PP population	
	Placebo	Circadin® 2 mg
Patients in population	86	76
Baseline (end of 2-week run-in period):		
N	86	75
Mean ± SD	60.93 ± 11.527	60.52 + 14.773
Range	28.2 – 86.3	13.7 – 92.0
End of 3-week double-blind period:		
N	86	74
Mean Change ± SD	-14.46 ± 17.324	-14.85 ± 19.378
Range	-56.4 – 31.7	-87.3 – 23.6
End of 2-week run-out period:		
N	85	74
Mean Change ± SD	-16.29 ± 18.149	-11.63 ± 18.718
Range	-62.9 – 33.3	-86.2 – 23.3

Similarly the "Awakening from Sleep" (AFS) parameter showed improvement in both groups, particularly the Circadin group, and in both populations, but not to the point of significance (p = 0.133 for the PP population).

Table 3 - AFS (in mm) and change in AFS, PP population (Neurim VII)

Visit	PP population	
	Placebo	Circadin® 2 mg
Patients in population	86	76
Baseline (end of 2-week run-in period):		
N	86	75
Mean ± SD	59.27 ± 12.673	61.47 ± 15.412
Range	11.3 – 81.2	6.3 – 95.0
End of 3-week double-blind period:		
N	86	74
Mean Change ± SD	-10.54 ± 18.516	-15.34 ± 21.658
Range	-63.3 – 33.8	85.0 – 26.1
End of 2-week run-out period:		
N	85	74
Mean Change ± SD	-12.52 ± 19.979	-11.71 ± 17.903
Range	-68.5 – 36.7	-83.2 – 25.8

The change in "Behaviour following Wakefulness" (BFW) was significantly improved in the Circadin group compared to placebo (p = 0.003 in the PP population) (Table 4)

Table 4 - BFW (in mm) and change in BFW, PP population (Neurim VII)

Visit	PP population	
	Placebo	Circadin® 2 mg
Patients in population	86	76
Baseline (end of 2-week run-in period):		
N	86	75
Mean ± SD	57.05 ± 15.360	60.42 ± 14.240
Range	5.6 – 84.1	30.8 – 95.0
End of 3-week double-blind period:		
N	86	74
Mean Change ± SD	-7.12 ± 16.047	-15.92 ± 20.450
Range	-53.2 – 35.0	-83.1 – 23.7
End of 2-week run-out period:		
N	85	74
Mean Change ± SD	-9.66 ± 18.544	-11.55 ± 17.225
Range	-52.8 – 40.6	-83.6 – 14.3

Neurim VIIIa

During the submission of Circadin trials to the EMEA, concerns were raised by the CPMP about the use of sleep questionnaires and a sleep diary to demonstrate primary efficacy in the pivotal trials. In particular, the CPMP's Scientific Advice Committee suggested the use of an active comparator to demonstrate assay sensitivity. In response to this advice, the sponsor conducted Neurim VIIIa, a multi-centre, double-blind, parallel-group placebo-controlled, randomized study comparing the efficacy of a standard dose of the well-known insomnia drug zolpidem and placebo, matching the patient selection criteria, assessment tools and treatment closely to the pivotal trial Neurim VII, described above. In this way the sponsor hoped to demonstrate the sensitivity and validity of the assessment tools used in the pivotal studies - especially the LSEQ and sleep diary.

The study was run from March 2003 to December 2003 across 43 sites in Belgium, France and Israel. An enrolment of 200 patients was planned in order to obtain 110 patients passing screening, but 289 were screened and 179 patients entered the study. Zolpidem demonstrated a statistically significant improvement over placebo in the primary efficacy measure, QON ($p = 0.003$). The result was significant for both the full analysis set and the PP population. Statistical significance was also found for zolpidem over placebo in many of the secondary measures of efficacy. A superior response was found for the LSEQ-derived parameters QOS ($p = 0.002$) and GTS ($p = 0.014$), respectively. There was no statistically significant improvement over placebo for AFS ($p = 0.24$) or BFW ($p = 0.2$) respectively. There was also no significant improvement in QOD ($p = 0.54$).

Neurim IX

This was a multi-centre, double-blind, randomized placebo-controlled parallel group trial of the efficacy and safety of Circadin 2mg in the improvement of sleep quality in patients aged at least 55 years with insomnia according to DSM-IV criteria. A number of Scottish sites were involved in the study, which ran from September 2004 to March 2005. A planned enrolment of 800 was hoped to allow at least 166 patients to complete three weeks of treatment in each arm with either Circadin or placebo. The design was similar to that of Neurim VIIIa, with a two-week period when all patients receiving single-blind placebo (run-in), followed by three weeks of double-blind treatment with either Circadin 2mg or placebo according to a 1:1 randomization. It differed from Neurim VIIIa in that there was no two-week wash-out period. Medication was self-administered as a single tablet two hours before the intended bed time. Statistical significance was found for the primary efficacy measure, an improvement of at least 10mm in both the QOS and BFW parameters of the LSEQ (Tables 5,6).

Table 5 - Primary efficacy endpoint, full analysis population (Neurim IX)

	Circadin		Placebo	
	N	%	N	%
Improvement of ≥ 10mm on the Leeds QOS and BFW scales				
Yes	44	(26%)	25	(15%)
No	124	(74%)	139	(85%)
Missing	1		1	

Odds-ratio for Circadin vs Placebo = 1.97 (1.14, 3.41)

Chi-square statistic = 6.04, P = 0.014

Data from one patient in each group was missing, but 44/169 (26%) patients receiving Circadin met this endpoint compared to 25/165 (15%) patients receiving placebo. Chi-square analysis suggests this is a significant difference ($p = 0.014$). Statistical significance ($p < 0.05$) was found for a number of secondary efficacy measures, including those pertinent to sleep quality, sleep latency, and daytime functioning. The improvements seen in the ITT population were maintained also in the PP population. In this study population, sleep quality appeared significantly improved by Circadin compared to placebo.

Table 6 – Sleep quality (LSEQ, QOS parameter), full analysis population (Neurim IX)

	Circadin		Placebo	
	Mean	(SD)	Mean	(SD)
Leeds Questionnaire (QOS)				
N	168		164	
Visit 2	54.5	(9.3)	53.7	(9.7)
Visit 3	45.9	(16.0)	49.5	(14.8)
Difference	-8.6	(16.3)	-4.2	(14.7)

Mean difference for Circadin vs Placebo = -4.0 (-7.2, -0.8)

P = 0.014

Efficacy Summary

- The special population studies were performed with small sample sizes and a heterogeneous mixture of inclusion criteria and efficacy endpoints, but generally support a therapeutic effect of Circadin in improving sleep quality.
- The Phase II dose-response studies (Neurim IV, Neurim V) did not contribute clear evidence of efficacy or provide clear evidence of dose-response.
- There was some evidence for continued efficacy of Circadin treatment over longer periods up to six and twelve months (Neurim V). While statistically significant, the result is derived from sleep diary analysis, whose validity as an outcome measure is unknown.
- The only Phase III trial to use objective sleep outcome measures (the sleep laboratory study Neurim I) did not find a statistically significant improvement in its primary efficacy measure for Circadin compared to placebo.
- The choice of primary efficacy endpoints in the pivotal studies is problematic. While the pivotal trials found statistical significance in their respective primary measures of efficacy, they were dissimilar (QOS, sleep diaries, QOS and BFW responder rates) and used components of previously validated instruments rather than the validated measures as a whole (LSEQ, PSQI).
- The use in a pivotal trial of a design which excludes placebo responders is a significant limitation and introduces the inclusion of selection bias.
- The pivotal trial Neurim VII demonstrated significant improvement in QOS under treatment with Circadin compared to placebo, although the upper end of its 95% confidence interval for treatment effect approached zero
- The active comparator trial (Neurim VIIIa) was not of optimal design; a placebo and active-controlled study with a non-inferiority analysis would be required to determine that Circadin and Zolpidem are comparably efficacious. It provided some evidence of correlation between previously validated outcome measures (PSQI components) and derived variables such as the QOS (LSEQ components) used as outcome measures in the pivotal trials.
- The pivotal trial Neurim IX found that significantly more patients receiving Circadin than placebo exhibited an improvement of at least 10mm in both the QOS and BFW parameters of the LSEQ.
- The Phase III trials, while not of optimal design, when taken together demonstrate modest efficacy for Circadin in improving sleep in the target population, those aged at least 55 with primary insomnia.

Safety

The safety analyses of the studies pertinent to Circadin included data collected from 1361 patients who were dosed at least once with the drug. At the proposed dose of 2mg, 373 patients were exposed for at least six months and 146 for 12 months. A total exposure of 15256 patient-weeks to Circadin, at all doses, was recorded. Most of the submitted studies, and all of the pivotal studies, were short-term interventions. Safety was assessed by a registry of adverse events, physical examination including vital signs (and in some cases, ECG), and laboratory parameters including full blood examination, biochemistry, liver function tests and

urinalysis. Withdrawal effects were considered of special interest and were investigated in the safety analyses of most of the clinical studies.

Pivotal Studies

Neurim VII

During the three-week double-blind treatment phase, the mean time of exposure to the study drug was 20.6 days; 146 patients (78%) received treatment between two and three weeks, and only four patients received treatment for less than two weeks.

The safety population for the study comprised 187 patients. Of these, 13 patients (7.0%) reported 15 adverse events before randomization. 18 patients (10%) reported 29 treatment-emergent adverse events during the double-blind phase, and 19 patients (10%) reported 19 adverse events during the wash-out phase. 11 of the 20 adverse events during the double-blind treatment period of the trial were mild, with the remainder moderate in severity. The most common adverse events were “body as a whole” followed by “gastrointestinal”. Of these adverse events, only four were considered at least possibly related to the study medication: one instance each of diarrhoea, headache, anxiety and somnolence. In all four instances, placebo was the drug given (Table 7).

Table 7 - Adverse events during the double-blind treatment period (Neurim VII)

	Placebo N=93		Circadin® 2 mg N=94		Total N=187	
	No. patients	No. events	No. patients	No. events	No. patients	No. events
All adverse events	9 (10%)	13	9 (10%)	16	18 (10%)	29
Body as a whole	2 (2%)	2	2 (2%)	2	4 (2%)	4
Gastro-intestinal system	1 (1%)	1	3 (3%)	3	4 (2%)	4
Diarrhoea	1 (1%)	1	1 (1%)	1	2 (1%)	2
Platelet, bleeding and clotting	1 (1%)	1	2 (2%)	2	3 (2%)	3
Haematuria	0	0	2 (2%)	2	2 (1%)	2
Urinary system	0	0	3 (3%)	4	3 (2%)	4
Urinary tract infection	0	0	2 (2%)	2	2 (1%)	2
Central and peripheral nervous system	0	0	2 (2%)	2	2 (1%)	2
Liver and biliary system	1 (1%)	1	1 (1%)	1	2 (1%)	2
Psychiatric	2 (2%)	2	0	0	2 (1%)	2
Skin and appendages	1 (1%)	1	1 (1%)	1	2 (1%)	2
Metabolic and nutritional	1 (1%)	2	0	0	1 (1%)	2
Musculoskeletal system	1 (1%)	1	0	0	1 (1%)	1
Myo endo pericardial & valve	1 (1%)	1	0	0	1 (1%)	1
Respiratory system	0	0	1 (1%)	1	1 (1%)	1
Secondary terms	1 (1%)	1	0	0	1 (1%)	1

No deaths occurred during the study. No serious adverse events were reported during the double-blind phase of the study. One patient experienced a mild worsening of chronic hypertension during the run-in phase. Another developed a recurrence of right-sided transient ischaemic event symptoms, six days after the conclusion of the study and was not considered a related to treatment.

Neurim VIIIa

This is not pertinent to the application to market Circadin since the drug was not used at any stage of this tria.l.

Neurim IX

453 patients were randomized and received at least one dose of study medication. During the double-blind treatment period, 55 patients receiving Circadin (24.4%) and 47 patients receiving placebo (20.6%) experienced at least one adverse event. Although this trial featured no wash-out or follow-up phase, significant and severe adverse events were sought up to 30 days after the completion of double-blind treatment, using telephone contact. No such events were recorded.

There was one adverse event classed as severe, this being “emotional distress” in a patient receiving Circadin. No deaths were recorded. One patient experienced a serious adverse event (non-specific cardiac chest pain) during the placebo run-in phase and was withdrawn from the study; this event was unlikely to be related to the study medication.

Extension Studies

Neurim V

During the double-blind treatment period (six weeks), 62 patients were exposed to Circadin 1mg, 65 to Circadin 2mg, and 67 to Circadin 5mg. The mean lengths of exposure in these groups were very similar, with a range of 41.3 days to 43.6 days. During the open-label

period, 112 patients completed six months of treatment with Circadin 2mg, and 96 patients completed 12 months of treatment with Circadin 2mg. The mean exposure at this dose in this period was 243.5 ± 109.9 days. The safety population for the double-blind treatment period included 263 patients. 93 patients (35%) reported an adverse event during double-blind treatment.

No deaths occurred at any stage of the study. Serious adverse events were rare, and totalled only nine for the duration of the study. Of these, one occurred during the single-blind placebo run-in phase; none occurred during double-blind treatment, and the remaining eight occurred during the open-label extension phase. The serious adverse events included duodenal sphincterotomy, surgery for venous insufficiency, four fractures (two resulting from falls), an acute myocardial infarction, syncope from aortic stenosis and cholecystitis. None was considered related to study treatment.

Other non-pivotal Studies

Neurim I

Although drug exposure is not explicitly stated in the study report, the study design was simple and all patients completed treatment, so the exposure may be presumed to be 20 patients to Circadin 2mg for three weeks. No deaths, serious or severe adverse events were reported in either treatment group.

Neurim IV

In this design, 428 patients were exposed to Circadin 2mg for three weeks (the V2, single-blind "run-in" period). 284 patients were exposed to six weeks of active treatment (at varying doses, as this was a dose-ranging study) and 113 were exposed to six weeks of active treatment with Circadin 2mg.

No patients died during the study, although two died after termination from pre-existing cardiovascular disease. Five patients experienced serious adverse events, thought to be unrelated to study treatment. These included cerebrovascular disease, severe hyperthyroidism, bladder cancer, acute limb ischaemia, and allergic reaction. Notably, the allergic reaction occurred during a placebo treatment period. Those considered at least possibly related to treatment with the study drug include mild liver function derangement, headache, mild leucopenia, moderate malaise, moderate diarrhoea, anxiety, and moderate insomnia. The most common adverse event was headache (7.01% during the V2 Circadin 2mg run-in period, compared to 6.56% during the V1 placebo wash-out period)

Pooled Safety Data

For the population receiving Circadin, the most frequent events were asthenia, back pain, headache, and respiratory infections, all of which could be considered common (frequency more than 1 in 100 but less than 1 in 10) in both the Circadin and placebo groups.

Clinical Summary and Conclusions

- Safety was evaluated in adequate numbers, in a population of 1361 patients who received at least a single dose of Circadin; 373 patients received the proposed dose for at least 6 months, and 146 received the drug for at least 12 month.
- Adverse events of any kind were no more common under Circadin therapy than with placebo. The most common adverse events reported were asthenia, headache, back pain and respiratory infections. When adjusted for exposure, all of these were more frequent in the placebo group than in those receiving Circadin.

- Three deaths occurred in patients exposed to Circadin, due to cardiopulmonary arrest, acute myocardial infarction and acute pulmonary oedema. None was considered related to drug treatment.
- Serious adverse events were not common. Of the 16 serious adverse events recorded, 13 occurred during treatment with Circadin. These involved a broad spectrum of body systems or events experienced. None was considered related to drug treatment.
- Adverse events leading to withdrawal were less frequent in patients treated with Circadin (17 cases, 1.3%) than among those treated with placebo (42 cases, 3.6%).
- No clinically significant changes were found under Circadin treatment in laboratory parameters, physical examination or vital signs.
- There was no data to suggest withdrawal or rebound phenomena; indeed for those studies that featured a wash-out period or withdrawal follow-up, sleep parameters tended to decline after ceasing treatment but often to values equivalent to, or better than, baseline.
- Circadin appears to be safe and well tolerated in the target population.

V. Pharmacovigilance Findings

There were no pharmacovigilance data in the submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the Delegate's overview and recommendation.

Quality

The quality evaluator has noted that the prolonged release property of Circadin is due to the excipient, ammonio methacrylate copolymer. The assay method used for the *in vitro-in vivo* correlation has been deemed unreliable. The quality evaluator has noted that the absence of a validly established IVIVC does not, in itself, render the application unapprovable, but any future changes to the formulation or method of manufacture would require increased scrutiny.

The *in vitro* dissolution rate of the tablets increases significantly in the presence of ethanol. It is likely that dose dumping would occur *in vivo* if the tablets were taken with alcohol.

The quality evaluator has noted that maximum melatonin levels achieved with Circadin are about 1200 pg/mL compared with endogenous levels of 10 mg/ mL during the day and 30 pg/ mL at night. There were significant problems with the method used to assay melatonin in the major bioavailability study. Quality control samples analysed throughout the course of the study gave assay results in the range 59% - 76% of the expected results. The sponsor has claimed that while inaccurate, the precision of the method was satisfactory.

This submission was last reviewed by the PSC on 27 July 2009 where additional data and comments provided by the sponsor and the TGA in relation to the deficiencies identified in the assay method used in the bioavailability study 22940 were considered. The Committee did not accept the sponsor's argument that satisfactory precision of the assay method should be used as a surrogate for an analytical method that yields consistently inaccurate quality control results. The PSC therefore supported the evaluator's recommendation that results of study 22940 be discounted given the seriousness of the identified deficiencies in the assay method used. The PSC concluded that in the event the Delegate recommends approval of this

application, the sponsor should be asked to remove the data obtained from study 22940 from the Product Information.

Non-Clinical

There were no nonclinical objections to registration. The evaluator noted that the data package was relatively comprehensive. Primary pharmacology studies of melatonin provided some, albeit limited, evidence of promotion of sleep onset in monkeys and sedative hypnotic activity in rodents. Melatonin metabolism was shown to be mediated by the hepatic enzymes CYP1A1, CYP1A2 and CYP2C19. Melatonin was able to inhibit CYP1A2 and CYP3A.

Toxicology studies were adequately conducted and sufficiently comprehensive to characterise the safety profile of melatonin, though toxicokinetic sampling was limited. The liver, thyroid and kidney were identified as target organs for toxicity at high (68x) no-effect exposure margins over those anticipated clinically.

The incidence of pituitary adenomas and thyroid follicular cell adenomas was increased in males in the rat carcinogenicity study. Although a no-effect dose was not established, the dose where tumorigenic responses occurred was *ca* 700x the clinical dose, based on body surface area. The genotoxicity profile of melatonin was negative, suggesting the carcinogenic liability of melatonin in humans is low.

Reproductive toxicity effects were limited to slight maternotoxicity in rats, increased incidences of growth impairment and developmental delays in rat pups and increased incidences of visceral and skeletal malformations/ variations in rabbit fetuses at high (45-900x) no-effect exposure margins over those anticipated clinically.

Clinical

Published literature provided additional information to supplement the pharmacokinetics and drug interactions of data for melatonin in Circadin. The absolute bioavailability of melatonin from Circadin tablets has not been determined. Melatonin is similarly bioavailable from Circadin and a melatonin solution. Published studies, using a different formulation of melatonin tablets demonstrated highly variable absolute bioavailability, in the region of 15% with a high-pass metabolism.

There were no dose-finding pharmacological studies using Circadin. In the clinical overview it was stated that Circadin 2 mg tablets were developed to provide a melatonin profile in the blood than more closely matched normal physiological release. Literature supported a nocturnal melatonin production rate of 10 – 80 µg/ night and that melatonin production occurred later and with a lesser peak in older subjects and was lower still in older adults with insomnia. In the Clinical Summary it was stated that the choice of dose was based on evidence of efficacy of 2 mg from early pilot studies and that a 2 mg dose of exogenous melatonin will produce approximately normal endogenous levels of melatonin in the cerebrospinal fluid. No data was submitted to show that Circadin dosed as proposed would result in physiological levels of melatonin in the CSF. Thus there is no clear connection between the proposed dose of Circadin and the physiological rate of production of melatonin.

In study 100, an increasing dose PK study, use of a ½ x Circadin 2mg tablet for the 1 mg dose has the potential to introduce dosing inaccuracy and to interfere with the matrix releasing mechanism. For this reason the EMEA considered that dose proportionality had not been conclusively established and this was stated in the EPAR to have contributed to the sponsor removing a claim to use doses higher than 2 mg from the SPC.

Three Phase 3 studies and a sleep laboratory study (Neurim 1) are considered pivotal. One of the Phase 3 studies (Neurim VIIIa) was an external comparator study (using zolpidem) to

validate the methodology of earlier studies. In all these studies patients had primary insomnia and were aged at least 55 years. Patients suffering from severe neurological, psychiatric or neurosurgical diseases or taking CNS medications including benzodiazepines were excluded.

The primary assessment tool in all studies was the Leeds Sleep Evaluation Questionnaire (LSEQ). This tool comprises 10 self-rating 100 mm-line analogue questions concerning aspects of sleep and early morning behaviour. It was developed and validated by Neurim Pharmaceuticals in its development program for Circadin. The 10 questions of the LSEQ measure ease of getting to sleep, quality of sleep, ease of waking from sleep and behaviour following waking (BFW). In the opinion of the evaluator, the use of elements of the LSEQ has not been externally validated.

The primary outcome variable in the pivotal clinical trials was quality of sleep (QOS), a subset of the LSEQ or a combination on QOS and BFW. Based on data from study Neurim IV it was considered that 10 mm improvement in VAS score for the LSEQ QOS was a clinically significant difference and this was used as the definition of a "responder". Other assessment instruments used were the Pittsburgh Sleep Quality Index (PSQI), a Somnitor™, a device to monitor sleep quality by measuring movement, polysomnography and neurocognitive testing.

Neurim 1 was a randomised, double-blind, parallel group, placebo-controlled study to assess the effects of Circadin 2 mg on the sleep-wake cycles of 40 patients aged ≥55 years with primary insomnia according to DSM-IV criteria. This study was conducted during 1996-97 and used polysomnography, LSEQ, vigilance and cognitive skills testing and the Somnitor. After a 2-week run-in period of single-blind, placebo treatment patients were randomised to 3 weeks of placebo (n=20) or Circadin (n=20) taken 1-2 h before bedtime. The study concluded with a 3 week withdrawal period. This study did not demonstrate a statistically significant change in the primary outcome variable of Duration of Wakenings After Sleep Onset (a polysomnographic measurement). Statistically significant differences, favouring Circadin were seen for sleep onset latency 7 minute reduction for Circadin vs. 1 minute for placebo), total duration of time awake prior to sleep onset (approx change from 18 to 11 minutes for Circadin and from 21 to 20 minutes for placebo) and time awake before sleep onset expressed as a % of total time asleep. There was a significant reduction in total reaction time for subjects given Circadin but no difference in other neurocognitive tests including "Tests of Everyday Attention" (TEA). These measures returned towards baseline on withdrawal of study drug.

No statistically significant treatment effects were seen for sleep architecture, all-night EEG parameters or the actigraphic parameters recorded by the Somnitor™. No treatment effects were seen in sleep diaries of the Circadin and placebo groups however 20% of patients given Circadin had "phase advance" or the desire to go to sleep earlier than at baseline.

Neurim VIIIa compared zolpidem with placebo and was used to validate efficacy measures. All 3 studies had a similar design to Neurim 1 but were conducted with out-patients who self-medicated, taking a single tablet (active or placebo) 1- 2 hours before the intended bedtime. The primary efficacy endpoint in Neurim VII was Quality of Sleep (QOS), derived as the mean of Questions 4 and 5 of the validated questionnaire (the Leeds Sleep Evaluation Questionnaire).

In Neurim IX the primary efficacy parameter was the response rate, with responders, defined as an improvement of 10 mm or more on both the Leeds QOS and behaviour following wakefulness (BFW) parameters. A change of 10 mm or more on each of these visual

analogue scales was considered to be clinically relevant. In the run in period subjects who responded to placebo, defined as a change of > 40 mm in the LSEQ-QOS were excluded from the primary efficacy analysis. Remaining subjects were then randomised to receive either Circadin 2 mg or placebo for 3 weeks (Neurim VII and IX).

In Neurim VII a total of 222 subjects were enrolled and 170 randomised to Circadin (n= 82) or placebo (n=88). There was a 22.48 mm change from baseline in the Circadin arm vs. 16.51 mm in the placebo arm for the LSEQ-QOS score. The difference of 5.97 mm was statistically significant (p=0.047) ITT analysis. In Neurim IX a total of 523 subjects were enrolled and 453 randomised with 334 included in the full analysis, Circadin (n= 169) and placebo (n= 165). The response rate (improvement in LSEQ-QOS & BFW $\geq$ 10mm) was 26% for Circadin vs. 15% for placebo (p=0.014).

In the opinion of the TGA, use of a subset of the LSEQ has not been validated, although the sponsor disagreed with this opinion. It was, however, a cause for concern during the application to market Circadin in Canada and Switzerland. Differences were statistically significant in study VII, VIIIa for both the PP and ITT populations and for the ITT population in study IX (PP results were not presented).

Secondary efficacy variables generally showed trends favouring Circadin and were statistically significant in favour of Circadin in studies VII and IX.

A total of 1361 patients received Circadin in the clinical trial program with 373 exposed for at least 6 months and 146 for l2 months. Three deaths (cardiopulmonary arrest, acute MI and acute pulmonary oedema) occurred during study and 13 serious adverse events were recorded, with none being considered related to study drug. There was no notable difference in the frequency of adverse events or laboratory abnormalities across treatment groups. The most frequent events were asthenia, headache, back pain and respiratory infections. All these events were more frequent in the placebo group than in subjects given Circadin Adverse events leading to withdrawal were less frequent in subjects given Circadin (n=17; 1.3%) than in subjects given placebo (n=42; 3.6%).

Melatonin has been extensively used as a dietary supplement in some countries for many years. The sponsor submitted no additional safety data concerning with exposure.

Risk-Benefit Analysis

The efficacy studies used a subset of a validated efficacy instrument which had not been externally validated. Modest differences from placebo and from baseline were apparent in the pivotal studies for the primary measures of efficacy with either a trend towards, or a statistically significant difference favouring Circadin for secondary efficacy measures. It is appropriate to restrict the indication to “poor quality of sleep” as there is no evidence that total sleep duration or time to onset of sleep is improved to a clinically significant extent by Circadin. Differences in quality of sleep could be detected by subjects with primary insomnia under controlled conditions so it is considered that degree of efficacy has been demonstrated. No safety concerns were apparent from short term use of Circadin.

Efficacy and safety of Circadin has not been assessed in patients with severe neurological, psychiatric or neurosurgical diseases or in subjects taking CNS medications including benzodiazepines.

Safety and efficacy of Circadin beyond 3 weeks has not been fully assessed. It is not clear if improved quality of sleep is maintained or if there are long term safety issues associated with this dose of exogenous melatonin. There are no safety signals apparent in the submitted data. Given that subjects were able to identify clinically and statistically significant improved

quality of sleep with Circadin and that no safety issues with short term treatment were apparent it is reasonable that Circadin be approved for use for short term treatment. More comprehensive safety data would be required to support longer term use. There are no data showing efficacy in combination with other hypnotic agents.

It was proposed to register Circadin for *short term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 years or over.*

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations and the Delegate's overview, were asked for the following advice:.

- whether the Indications should include a statement that a clinically significant increase in duration of sleep or time to onset of sleep with Circadin has not been demonstrated or whether this should be included only in the Clinical Trials section.
- Whether it is appropriate to restrict duration of use to short term, given the physiological reduction in melatonin production is long term. Should a maximum duration for an episode of use be specified?
- Whether the Indications should restrict use to monotherapy treatment.

ADEC agreed on restrictions on both duration and monotherapy and recommended approval for the indication:

> *Monotherapy for the short term treatment (up to three weeks) of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.*

In making this recommendation, the ADEC considered that the available data indicate melatonin use is associated with a modest benefit in improving quality of sleep when used as monotherapy. The ADEC considers the available data are 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 study, Neurim VII. Changes to the Product Information which should be made prior to approval include that the data obtained from study 22940 should be removed, as recommended by the PSC in its review on 27 July 2009.

Outcome

Based on review of quality, safety and efficacy data, TGA approves the registration of Circadin, melatonin 2mg prolonged release tablets blister packs, indicated for:

Monotherapy for the short term treatment (up to 3 weeks) of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over.

Attachment 1. Product Information

Product Information

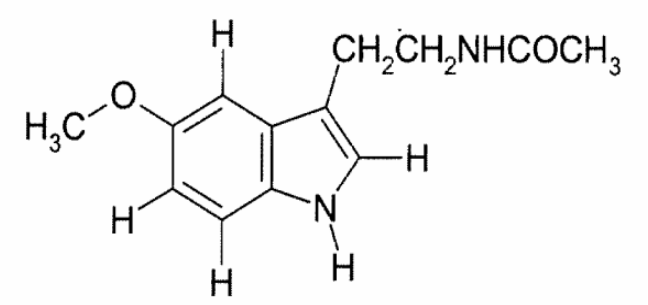
Circadin® Prolonged Release Tablets

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 melatonin. 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 are 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.

In an open study where 96 subjects completed 12 months treatment with Circadin no tolerance, rebound or withdrawal effects were reported. Efficacy of Circadin in long term use has not been adequately assessed in placebo controlled studies.

Indications

Monotherapy for the short term treatment (up to three weeks) 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 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.

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 1361 patients were taking Circadin and 1247 patients were taking placebo), 37.0% of patients receiving Circadin reported an adverse reaction compared with 31.8% taking placebo. Comparing the rate of patients with adverse reactions per 100 patient weeks, the rate was higher for placebo than Circadin (placebo-8.21 vs. Circadin-3.17). The most common adverse reactions were headache, pharyngitis, back pain, and asthenia, which were common, by MedDRA definition, in both the Circadin and placebo treated groups. In the Circadin group, there were 17 cases (1.3% of the safety population) of adverse events leading to discontinuation of the patient versus 42 cases (3.6% of the safety population) of adverse events leading to discontinuation of the patient, in the placebo group.

Overall Adverse Experience for adverse events occurring with a frequency ≥ 1%

Body System/Adverse Experience	**Circadin % (N=1361)**	**Placebo % (N=1247)**
Body as a Whole		
Abdominal Pain	1.8	1.9
Asthenia	3.1	1.9
Back Pain	3.2	1.4
Flu Syndrome	1.1	0.6
Headache	5.2	6.2
Infection	1.5	0.6
Neck Pain	1.0	0.6
Pain	1.6	1.0
Cadiovascular		
Migraine	1.3	1.3
Digestive		
Constipation	1.1	0.6
Diarrhoea	1.3	1.2
Nausea	1.5	1.4
Musculoskeletal		
Arthralgia	1.3	0.8
Nervous		
Abnormal Dreams	1.1	2.6
Anxiety	1.3	1.4
Dizziness	1.6	1.4
Respiratory		
Bronchitis	2.1	1.1
Cough increased	1.1	0.9
Pharyngitis	4.6	2.2
Rhinitis	2.2	2.1
Sinusitis	1.0	0.2

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 6.9% of subjects receiving Circadin reported an adverse reaction compared with 5.9% 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
Metabolism and Nutrition Disorders		Hypertriglyceridaemia
Psychiatric Disorders	Irritability, Nervousness, Restlessness, Insomnia, Abnormal dreams	Mood altered, Aggression, Agitation, Crying, Early morning awakening, Libido increased
Nervous System Disorders	Migraine, Psychomotor hyperactivity, Dizziness, Somnolence	Memory impairment, Disturbance in attention, Poor quality sleep
Eye Disorders		Visual acuity reduced, Vision blurred, Lacrimation increased
Ear and Labyrinth Disorders		Vertigo positional
Vascular Disorders		Hot flush
Gastrointestinal Disorders	Abdominal pain, Constipation, Dry mouth	Gastrointestinal disorder, Gastrointestinal upset, Vomiting, Bowel sounds abnormal, Flatulence, Salivary hypersecretion, Halitosis
Hepatobiliary Disorders	Hyperbilirubinaemia	Hepatic enzyme increased, Liver function test abnormal, laboratory test abnormal
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	Eczema, Erythema, Rash pruritic, Pruritus, Dry skin, Nail disorder, Night sweats,
Musculoskeletal and Connective Tissue Disorders		Muscle cramp, Neck pain
Reproductive System and Breast Disorders		Priapism
General Disorders and Administration Site Conditions	Asthenia	Fatigue
Investigations	Weight increased	

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 should be continued for a minimum of three 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 Tablets. AUST R: 244390

Storage conditions

Store below 25ºC. Protect from light

Name and address of the sponsor

Sponsor:
Commercial Eyes Pty Ltd.
Suite 6 651 Victoria Street
Abbotsford
VIC 3067
Australia

Distributor:
Lundbeck Australia Pty Ltd
1/10 Inglewood Place
Norwest Business Park
Baulkham Hills NSW 2153
Ph: +61 2 9836 1655

Poisons schedule of the medicine

S.4.

Date of approval:

28 October 2009

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Therapeutic Goods Administration

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