European Medicines Agency
Evaluation of Medicines for Human Use

ASSESSMENT REPORT
FOR
CIRCADIN

International Nonproprietary Name:
melatonin

Procedure No. EMEA/H/C/695

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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Introduction

Melatonin, the hormone produced by the pineal gland, plays an important role in the regulation of circadian rhythms. In humans the most important circadian rhythms is the sleep-wake cycle.

The sleep-wake cycle may be pathologically affected in different ways. Furthermore, the sleep may also be disturbed by various processes. The disturbances of the sleep-wake cycle are called circadian rhythms disorders and include the jet lag (tome zone change) syndrome, shift work sleep disorder, advanced sleep phase syndrome, non-24h sleep-wake syndrome. In all these insomnia might appear as a symptom. Chronic insomnia is itself a sleep disorder, in spite of being very complex. Transiently difficulty in sleeping is a vastly more common phenomenon than is chronic insomnia. The diagnosis of chronic insomnia is based on the subjective complaint of difficulty in initiating or maintaining sleep or of non-restorative sleep (not feeling well-rested after sleep that is apparently adequate in amount).

Primary insomnia

Primary insomnia is sleeplessness that is not attributable to a medical, psychiatric, or environmental cause. The diagnostic criteria for primary insomnia from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) is as follows:

- The predominant symptom is difficulty initiating or maintaining sleep or nonrestorative sleep for at least 1 month.
- The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or parasomnia.
- The disturbance does not occur exclusively during the course of another mental disorder (e.g., major depressive disorder, generalized anxiety disorder, delirium).
- The disturbance is not due to the direct physiologic effects of a substance (e.g., drug abuse, medication) or a general medical condition.

Physiological role of melatonin

Melatonin (N-acetyl-5 methoxytryptamine) is a neurohormone that is primarily produced in the pineal gland, located behind the third ventricle in the brain with daily and seasonal rhythms mainly under the control of the circadian oscillator located in the suprachiasmatic nuclei of the hypothalamus (SCN) which have melatonin receptors (Weaver et al., 1993). The pineal gland is a major component of the endocrine system that allows mammals to respond to the annual changes in photoperiod by adaptive alterations of their physiological state. Melatonin is synthesized in the pineal gland during the dark phase of the light/dark cycle and is rapidly delivered to the body via the systemic circulation. In addition to the pineal gland, melatonin is synthesized in several other structures (retina, Harderian gland, gut) where the genetic expression and biochemical activity of the melatonin-synthesizing enzymes have been detected. It has been proposed that melatonin plays an auto/paracrine role in these structures.

Studies performed to understand the mechanisms of action of melatonin in the regulation of some seasonal and circadian functions have demonstrated that the dynamic pattern of melatonin secretion is fundamental for its time-giving function.
The rhythmic pattern of melatonin secretion is important because it brings to organisms information about time that allows them to adapt some of their physiological functions to the daily and seasonal variations of their environment. It is thus necessary to delineate the various processes and elements that regulate the rhythms of melatonin synthesis and secretion to understand how environmental factors are transmitted to the whole organism.

About the product

Tryptophan is converted to serotonin (5-hydroxytryptamine), then acetylated (N-acetylserotonin) and finally converted to melatonin which is an indole ((N-acetyl-5 methoxytryptamine).

The pharmaceutical formulation is a prolonged release formulation of melatonin presented in 2 mg tablets.

The claimed therapeutic indication for Circadin was: *"The relief of primary insomnia characterized by poor quality of sleep in patients aged 55 or over*."

The indication agreed by the CHMP is: *Circadin is indicated as monotherapy for the short-term treatment of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over.*

The development programme/Compliance with Scientific Advice.

The first MAA for Circadin was submitted on 14 February 2000 and the application was withdrawn on 10 January 2002. The major objection mentioned in the CPMP consolidated list of questions issued on October 2000, was related to the efficacy as "the efficacy of Circadin in primary insomnia had not been demonstrated " because:

a) The three pivotal studies included in the first application(Neurim I, Neurim IV and Neurim V) were inconclusive.
b) Post –hoc analysis were just hypothesis generating,
c) Meta-analysis had several weaknesses: search and selection of studies included was unclear; studies sponsored by the applicant were merged and sensitivity analysis was not conducted; the results produced were very modest and its clinical relevance doubtful,
d) Dose-response relationship with the controlled-release formulation of Circadin was not established,
e) The validity of selecting only questions 4 and 5 of the Leeds Sleep Questionnaire as main efficacy variable was insufficiently justified and
f) The clinical relevance of changes in the QOS scale observed was questioned.

Following the Company's response to the LOI and the CPMP hearing which took place on 12 December 2001, the major objection related to the proof of efficacy was not solved during the discussion at the CPMP plenary meeting. The Company after discussion with the rapporteurs decided to withdraw the MAA and to request a Scientific Advice.

The Scientific Advice was requested in 2002 regarding the Phase III clinical development. The questions asked in relation to the intended indication for the treatment of primary insomnia were related to the:

-assessment of effect on insomnia [sleep quality/quantity/duration]
-use of non-restorative sleep as target of drug treatment
-inclusion criteria [DSM-IV and ICD-10]; >55 years
-primary outcome assessment of sleep quality with diary cards
-definition of clinically meaningful effect/clinical relevance
-secondary outcome variable
-assessment of withdrawal effect
-safety database

To confirm these results the applicant was advised by CHMP to conduct a further pivotal study that would be ideally 3 arms with and active control arm. The applicant chose to do otherwise. Two independent trials, although run in the same trial conditions were executed one to compare zolpidem 10 mg to placebo (Neurim VIIIa) and the other, the real pivotal study, to compare Circadin 2 mg to placebo (Neurim IX). See discussion in clinical efficacy section.

The new dossier includes all the data that were submitted in the first MAA and additional data extracted from the new studies performed during 2003-2005.

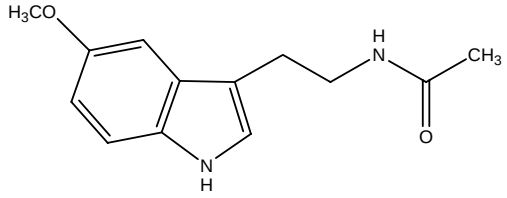
1. Quality aspects

Introduction

Circadin is presented in the form of prolonged-release tablets containing 2 mg of melatonin for oral administration. The excipients used in the formulation of Circadin are ammonio methacrylate copolymer Type B, calcium hydrogen phosphate dihydrate, lactose monohydrate, colloidal anhydrous silica, talcum and magnesium stearate. There are no novel excipients used in the formulation.

Drug Substance (to be changed in the EPAR to "Active Substance")

Melatonin has a relative molecular mass of 232.27 and the following structural formula:



Melatonin is a slightly off-white, crystalline powder, which is soluble in tetrahydrofuran and methanol, slightly soluble in ethyl acetate and insoluble in water.

- Manufacture

Melatonin is chemically manufactured by two manufacturers via organic synthesis starting from 5-methoxytryptamine. The route of synthesis consists of three steps starting with the reaction of 5-methoxytryptamine with acetic anhydride in ethyl acetate to yield crude melatonin, followed by the recrystallization from tetrahydrofuran to yield pure melatonin (purification step). The last step consists of micronisation of the pure melatonin to yield the final bulk melatonin with a particle size of less than 21µm.

Melatonin was characterised by Infrared spectroscopy (IR), proton NMR, carbon NMR, mass spectroscopy (MS) and elemental analysis.

- Specification

The specifications for the active substance include description (visual appearance), identification (melting point, IR, UV and HPLC), assay (HPLC), water content, total microbial count, heavy metals, impurities (HPLC and GC) and particle size distribution (laser method).

Five batches of the active substance were manufactured at production scale. The results showed that the active substance could be reproducibly manufactured.

The analytical methods have been adequately validated according to the ICH guideline on "Validation of Analytical Methods". The assay method for the active substance by potentiometry was validated with respect to linearity and precision The HPLC method used for determination of the impurities content was validated with respect to the specificity, detection and quantitation limits for the specified impurity 5-methoxytryptamine. The linearity, accuracy and precision were also assessed for this single specified impurity. The head-space gas chromatography method was validated regarding accuracy, inter-assay precision, specificity, linearity and range.

- Stability

Stability studies were performed on melatonin stored in the proposed packaging, according to the ICH guideline. Stability data (36 months long term 25°C/60% RH; 36 months accelerated 40°C/75%RH) was provided on three batches manufactured at both intended sites of manufacture.

The data provided is sufficient to confirm the proposed re-test period for each of the manufacturing sites.

Drug Product

- Pharmaceutical Development

Since melatonin presents an in vivo half-life of 40-50 min in humans, a prolonged-release dosage form was developed to obtain an 8 to 10-hour period of release of melatonin.

The formulation development involved the use of different methacrylate resins. The *in vitro* release properties of the formulations were evaluated. The *in vivo* release profile of the selected formulations was then tested against a regular release formulation in a healthy male volunteer at 10.00 am when endogenous circulating melatonin levels are low. *In vivo* release was evaluated by monitoring the urinary excretion of the major metabolite, 6-sulphatoxymelatonin (6-SMT). The two selected formulations and the regular release formulation were then further tested in a double-blind cross-over study in elderly healthy patients. Urinary excretion of 6-SMT occurred in a formulation-dependent manner and one formulation exhibited profiles, which essentially mimicked the endogenous metabolite excretion pattern.

During the scale up process the dimensions of the tablet (weight, diameter) and the proportions of excipients were modified. In addition, silicon dioxide was added to achieve a similar dissolution profile to the commercial tablet, with physical characteristics (hardness, friability) that complied with the requested commercial standards.

An *in vitro-in vivo* correlation was also established. A single-dose, two-way crossover comparative pharmacokinetic and food interaction study together with the corresponding *in vitro* dissolution study, were performed to establish an *in vitro-in vivo* correlation. The data showed linear correlation (level A), confirming that the proposed dissolution test may be considered a reliable marker for the *in vivo* performance.

- Adventitious Agents

Lactose monohydrate was of animal origin. A declaration from the lactose supplier was provided stating that the lactose was sourced from healthy animals under the same conditions as milk collected for human consumption. The magnesium stearate used was of vegetable origin.

- Manufacture of the Product

The manufacturing process for Circadin uses standard pharmaceutical techniques for a prolonged-release formulation. Manufacturing of the product comprises standard milling, blending, granulation steps, prior to compression.

Process validation was carried out on three batches of 600,000 tablets (102 kg batch size) and showed that the tablets can be manufactured reproducibly according to the finished product specifications.

- Product Specification

The product specifications include methods for appearance, dimensions, identity (HPLC – retention time), microbial purity, uniformity of mass, uniformity of content (HPLC), tablet hardness, assay (HPLC), residual solvents (methanol by GC), dissolution and impurities (HPLC). The dissolution is a 6-point test between 1 to 10 hours to define the profile.

The drug product specifications have been justified and all methods of analysis have been described and adequately validated.

- Stability of the Product

Stability data on six batches (manufacturing scale) was provided. Two batches were stored at 25°C/60% RH for 24 months and 60 months, other two batches at 30°C/70% RH for 12 months, and other two batches at 40°C/75%RH for 6 months. The following parameters were tested at every time interval: appearance, tablet weight, hardness, assay, individual and total impurities and dissolution profile. Loss on drying was determined after 12 months storage at 25°C/60% RH and microbial purity was determined after 9 months at 25°C/60% RH (first set of batches) and after 12 months at 30°C/70% RH (second set of batches).

Based on the available stability data, the proposed shelf life and storage conditions, as stated in the SPC, are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of test carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. A robust 6-point *in vitro* dissolution test has been developed to ensure batch-to-batch consistency. In addition, a linear level A *in vitro-in vivo* correlation was established confirming that the proposed dissolution test developed may be considered a reliable marker for the *in vivo* performance of the drug product.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow-Up Measures after the opinion, within an agreed timeframe.

2. Non-clinical aspects

Pharmacology

With the exception of two studies conducted by the Applicant to investigate the effects of melatonin on hexobarbital narcosis in mice and on brain melatonin and benzodiazepine binding sites in rats, all documentation concerning the primary, secondary and safety pharmacodynamics and pharmacodynamic interactions are derived from the published literature.

- Primary pharmacodynamics

While the current understanding of endogenous melatonin is substantial, especially regarding melatonin's involvement in the circadian timing system, the putative role that endogenous melatonin may play in regulating sleep and how this role is mediated remains unclear.

In vitro studies
Melatonin is described in the literature as acting at the central nervous system level, modulating the synchronisation of the biological clock and promoting sleep through stabilisation and phase-shifting effects on the suprachiasmatic nucleus of the hypothalamus.
Interaction with melatonin MT1 and MT2 receptor subtypes seem to be involved in the action.
MT1 receptors are located mainly in cells of he pituitary pars tuberalis (PT), controlling seasonal prolactin variations in ruminants, whereas there is no evidence to suggest that MT2 receptors are present in the PT. By contrast, both MT1 and MT2 receptors are located in the suprachiasmatic nucleus. The molecule ^{125}I-melatonin has been used in binding and autoradiographic studies and has enabled detection of melatonin binding sites expressed at low density in most tissues in which effect of melatonin have been reported.

The transduction pathways mediated by these melatonin receptors remain an unsolved and complex issue. The MT1 receptor couples to different G protein, one of which mediates inhibition of adenyl cyclase and the other activates phopsholipase Cβ. The MT2 receptor couples to phosphoinositide production, the inhibition of adenyl cyclase and the inhibition of the soluble guanylyl cyclase pathway. The MT2 receptor mRNA present in human retina and brain is responsible for entrainment of circadian rhythms in the SCN. MT1 and MT2 polymorphisms have been found in humans and may be associated with sleep disorders.

In vivo studies

In mammals melatonin is mainly synthesised in the pineal gland from serotonin but it also is formed in the gut and retina. The production is circadian and it is stimulated by photic stimulus arising after the onset of darkness. The peak of melatonin levels is reached in the middle of the night (between 2-4 a.m.) and decrease to low levels in the second half of the night. In young adults the average daytime levels of melatonin are 10 pg/ml and the peak nighttime level is 60 pg/ml. Endogenous production of melatonin is reduced in the elderly.

A limitation of studies in nocturnal laboratory animals is that melatonin is often administered during the light phase, when melatonin is not endogenously produced but the animals are most likely asleep. Nevertheless, rats display intermittent periods of sleep and wakefulness in both light and dark phases rather than a single consolidated sleep period such as observed in humans. This situation clearly has no analogue in humans; therefore the conclusions drawn from laboratory studies in rats may be of limited value when extrapolated to other species. In addition, the doses typically employed in rats (i.e. 2–20 mg/kg*) produce pharmacological circulating levels, several orders of magnitude greater than what is observed naturally, so like many of the human studies these may not reflect the endogenous physiological role of the hormone.

To explore the nature of sleep-promoting effects of melatonin, some authors initiated studies in diurnal macaques (Zhdanova et al, 1998). In addition to the phylogenetic proximity, there are several important similarities between humans and diurnal non-human primates, favouring the use of these animals to model normal and pathological sleep-related processes. Those include: (1) Similar temporal patterns of activation of the major circadian pacemaker, the SCN, relative to the rest-activity cycle in both species, i.e. high activity of the SCN neurons during the day correlates with these species' daytime activity, in contrast to nocturnal animals whose SCN is active during their daytime rest period; (2) Similar temporal patterns of melatonin production, occurring during habitual nighttime sleep period; (3) A consolidated nocturnal sleep episode, with similar sleep architecture, in contrast to the majority of nocturnal or diurnal species which tend to have a polyphasic sleep pattern. In all three species of diurnal macaques studied, the sleep process showed high sensitivity to daytime melatonin administration. Sleep initiation was significantly promoted by a wide range of melatonin doses used and, as in humans, showed a lack of dose dependence of the effect, once the dose (5–20 μg/kg, orally) was sufficient to induce physiologic circulating levels of the hormone (above 50 pg/ml). Lower doses failed to promote sleep in the macaques studied.

The Applicant has conducted two studies to investigate the primary pharmacodynamic profile of melatonin focussed on sleep induction.

1 - Effects of melatonin on hexobarbital-induced narcosis in mice

The effect of melatonin on hexobarbital (75 mg/kg, i.p.)-induced narcosis was investigated in mice using 20 mg/kg* melatonin i.p. (low dose) and 100 mg/kg* melatonin i.p. (high dose). The onset time for hypnosis and the duration of the sleeping period were measured in all groups. The results are exposed in the Table below:

Groups	Hypnotic onset time (min.)	Sleeping time (min).
Control	2.18±0.74	28.8±13.22
20 mg/Kg, ip	5.08±2.09*	43.94±12.52
100 mg/Kg, ip	2.47±1.46	78.51±19.46**

*P<0.05; **P<0.01.

The results show that melatonin, at the dose of 20 mg/Kg delayed the hypnosis induced by hexobarbital and increased the sleeping time of the animals. Furthermore the animals showed excitation and body rotation before following asleep. For the animals treated with the dose of 100 mg/Kg the duration of the sleeping period increased and the onset time for hypnosis was similar (slightly higher) to the one from controls. The results seem to suggest that melatonin potentiated the sleeping effect induced by hexobarbital, but increased the onset time for hypnosis (vs controls) for which a plausible explanation was not provided.
These effects are difficult to interpret and extrapolation to man cannot explain the efficacy of the proposed human dose of 2mg. In a study performed in 2 monkeys (from the literature) 5 µg/Kg of melatonin administered 2 hours before the onset of darkness was the minimum effective dose to promote sleep onset. The plasma levels obtained were similar to the physiological ones in that species (54 pg/ml). Therefore, the efficacy of melatonin is based mainly on clinical information.

2 - Reciprocal effects of chronic diazepam and melatonin on brain melatonin and benzodiazepine binding sites in rats
The effect of diazepan on the binding profile of ^{125}I iodomelatonin binding and the effect of melatonin administered in the drinking water on the benzodiazepine and ^{125}I iodomelatonin binding were evaluated in sinaptosomes prepared from the medulla pons and cortex of male CD rats aged 2 months. It was observed that melatonin via drinking water significantly enhanced benzodiazepine (^{3}H-RO 15-1788) binding in the medulla pons and slightly reduced it in the cortex, but did not affect ^{125}I-melatonin binding.
Daily injections of diazepam during 3 weeks reduced markedly ^{125}I-melatonin binding site density in the medulla-ponds but not in the cortex of male rats, whereas benzodiazepine binding was not significantly affected.
The combination of melatonin and diazepam reversed the suppression by diazepam of ^{125}I-iodomelatonin in the medulla-pons and the suppression by melatonin of benzodiazepine binding in the cerebral cortex.

- Secondary pharmacodynamics and Safety pharmacology

Nervous system
In mice, the Irwin test showed that at doses >8mg/Kg melatonin had no behavioural effects. At 16 mg/Kg a slight sedation was observed. Such sedation was also reported in the repeated dose studies conducted by the Company in rats. At doses of 64, 128 and 256 mg/Kg decreased fear, reactivity, muscle tone and hypothermia were observed with dose-dependent intensity and duration. At 128 mg/Kg it also showed analgesic activity in the four-plate test (Guardiola-Lemaitre et al., 1992, *Pharmacology Biochemistry and Behaviour, 41, 405*).
Daily administration of 2.5-10mg/Kg melatonin prior to the swimming test significantly reversed the increased immobility period that was observed on chronic exposure to swimming test. This effect was reported to be comparable with that of GABA-benzodiazepine (BZ) receptor agonists, appearing to involve GABA-benzodiazepine receptors (Raghavendra et al., *Eur. Neuropsychofarmacol.*10(6):473).
In other studies, acute administration of melatonin did not reveal antidepressant activity.

Endocrine and reproductive systems
Melatonin regulates pubertal development in some juvenile mammals. In seasonal breeders, melatonin seems to act as either pro-gonadotrophic or as anti-gonadotrophic according to the period of the year (autumn-winter/short days or spring-summer/long days respectively.
Melatonin has also been shown to influence secretion of several hormones in animals and in humans in some situations, namely the LH and prolactin, corticosteroids, thyroid hormones and insulin.
In rats administered 0.1 mg/Kg melatonin s.c. for 4 weeks, Olivares et al.(1989) *Arch. Biol. Med. Exp., 22, 378,* observed abnormal progression of spermatogenesis coupled to a decreased production of testosterone by Leydig cells, which were considered as secondary to a decrease in LH hormone production resulting in an impairment of the Leydig cell function. In female rats Liu and Meites (1973) *Endocrinology, 93, 152,* observed that a single intravenous dose of melatonin increased serum

prolactin levels. In Syrian hamsters several authors observed either decrease or an increase of the prolactin, FSH and LH hormones. It is possible that the conditions of administration such as the period of the year or the time of the day, the duration of the administration period may have influenced the results.
In hamsters, endogenous and cyclically administered melatonin (0.0025-0.025 µg) depressed the thyroid function. Melatonin given to blinded hamsters for 10 weeks in the drinking water partially restored thyroxin levels and testis weights normally associated with blinding.

Cardiovascular and respiratory systems
Melatonin receptors were identified on the anterior cerebral and caudal arteries of rats and on the coronary and pulmonary arteries of pigs.
In rats, a dose-related fall of mean arterial pressure, heart rate and also of brain serotonin release were observed in consequence of 30-60 mg/Kg melatonin i.v. Bradicardia was abolished by pre-treatment with bilateral vagotomy thus suggesting that it may be mediated through a parasympathetic action. (Chuang et al., 1993, *Pharmacology, 47, 91*).
Also studies in porcine and coronary arteries suggest the potential for melatonin to have tensive effects (Viswanathan et al., 1992 *Neuroendocrinology, 56, 864*; Weekley, 1993, *Pulmonary Pharmacol., 6, 149*). In baboons, 0.3 to 0.4 mg/Kg melatonin, i.v. caused a statistically significant increase of the cardiac output and ventricular ejection associated to a reduction in heart rate (Bosman et al., 1991, *J.Pineal Res.24, 62*).
The Applicant has submitted an evaluation of the cardiovascular and respiratory effects in rats. At a dose of 100 mg/Kg a slight decrease of heart rate and blood pressure were observed. The Q-T interval of the ECG and the respiratory rate were not changed. Also in humans the evaluation of ECG was performed and reported as not presenting any effects on the Q-T interval.

- Pharmacodynamic drug interactions

In the literature review provided, the secretion of melatonin has been shown to be affected by adrenergic agonists and antagonists, antidepressants, opiate agonists and antagonists, prostaglandin synthesis inhibitors, benzodiazepines, barbiturates and glucocorticoides.
In humans, co-administration of Circadin with thioridazine, imipramine and zolpidem showed pharmacodynamic interaction (increased sedation), with no pharmacokinetic interaction, while co-administration with cimetidine had no pharmacodynamic interaction but increased plasma melatonin concentration. This is reflected in the SPC (section 4.5)

Pharmacokinetics

Pharmacokinetic studies of exogenous melatonin in animals are available in the literature. The Applicant has conducted toxicity studies in the rats, dogs, and rabbits from which toxicokinetic data are obtained.
In toxicokinetics, plasma levels of melatonin were analysed in rat studies by a validated LC-MS/MS method with lower limit of quantification (LLOQ) 20ng/ml. In the rabbit an LC-MS method was used with LLOQ 20ng/ml. In the dog a validated radioimmunoassay (RIA) was used.

Absorption and bioavailability
In the study of Yeleswaram et al (1997) the pharmacokinetics and bioavailability of melatonin was investigated in rats, dogs and monkeys after p.o. and i.v. administration. The results are shown in the Table below:

Parameter	SD rat	Beagle dog	Cynom. monkey
Intravenous administration			
Dose (mg/kg*)	5.00	2.95	2.98
AUC (mg.h/l)	2.38	0.81	1.78
Clearance (L/h/Kg	2.11	3.84	1.68
Half-life (h)	0.33	0.31	0.57

Vd_{ss} (l/Kg)	1.05	1.48		1.20
Per os administration				
Dose (mg/kg*)	10.00	0.98	10.3	10.00
AUC (mg.h/l)	2.49	0.05	3.44	8.85
Bioavailability	53.5	16.9	>100	>100

The mean oral bioavailability of 10 mg/kg of melatonin was 53.5% in rats and >100% in dogs and monkeys. The low bioavailability (16.9%) in low doses (1mg/kg) in dogs suggests non-linear pharmacokinetics in experimental animals and also in humans, probably as a result of first-pass metabolism in the liver.

Distribution

Melatonin seems to distribute fast through tissues and even after brain injection is was shown, in rats, to clear after 5 minutes. The steady state distribution volumes in animals range between 1.05 and 1.48 L/Kg, with a typical value of 0.55 l/Kg in man (0.6-1.0) at doses of 5-10 and 0.08-0.15 µg/Kg, respectively.

Literature data show that in rat and humans most circulating melatonin is bound to albumin. It seems also to bind to haemoglobin and calmodulin.

Metabolism

According to available data, melatonin appears to be mainly metabolised by CYP1A1 and CYP1A2. From the chromatographic analysis of urinary metabolites obtained in rats administered i.v. with labelled melatonin three peaks were identified, two of them corresponded to the glucoronic and sulphate conjugates of 6-hydroximelatonin and the third compound was not completely characterised. The major metabolite accounting for 70%-80% of the radioactivity was the sulphate conjugate of 6-hydroxymelatonin whereas the glucoronic acid conjugate represented 5%. The unidentified metabolite corresponded to 12% of radioactivity.

In vitro metabolism studies using liver microsomes also indicates that 6-hydroxylation is the major route. Also 5-methoxyindoleacetic acid appears to be formed by de-acetylation of melatonin followed by de-amination.

Elimination and excretion

The main excretion route of the melatonin metabolites is renal. In rats administered i.v. with labelled melatonin, after a 48 hour collection of urine and faeces, the total amount of radioactivity in urine was 60%-70% of the administered melatonin and about 15% was found in faeces.

Toxicology

Applicant's own data together with literature data are available on acute toxicity, repeated dose toxicity, reproductive toxicity, genotoxicity and carcinogenicity.

- Single dose toxicity

Data from literature points towards a low acute toxicological profile by the oral route, with very high LD50 values as determined in rodents (1250 mg/kg and >3200 mg/kg respectively in mice and rats). The intravenous LD50 is 180 mg/kg to 472 mg/kg in mice and 356 mg/kg in rats. The main effects observed at high doses were sedation, lethargy, and vasodilatation. The higher doses led to impairment of righting, placing and flexor reflexes, marked reduction in body temperature and respiratory distress preceding death.

- Repeat dose toxicity (with toxicokinetics)

The toxicity of melatonin after repeated administration was evaluated in the rat and in the dog in company-sponsored studies.

In **rats**, the toxicological profile of melatonin after 90-day period of administration was low but very low doses were used in the study (0.3, 1.2 and 6 mg/kg/day). The toxicokinetic data from the study showed plasma concentrations up to 40 pg/ml, which are lower than those expected to be reached in humans, but the time of sampling is not specified. In this study the only melatonin-related effect reported was a decreased body weight gain of the animals at mid (males) and high doses (males and females). Also decreased testis and increased kidney relative weights were observed at high dose.

A combined 13-week study in rat with a 4-week recovery period coupled to a 26-week toxicity and a 104-weeks carcinogenicity phase was submitted in the dossier. The oral dose levels used in this study were 0, 15, 75 and150 mg/kg/day).

In the 13-weeks and the 26 weeks studies increased haemoglobin concentration and platelet counts were observed at 75 and 150 mg/Kg/day treated animals. Increased liver weights with minor centrilobular hepatocytic hypertrophy were observed. Increased testes, prostate and epididymides weights were seen in mid and high dosed males. Toxicokinetics showed that the systemic exposures of the animals were much higher than that expected during human therapeutics.
At 26 weeks, macroscopically dark thyroid was also recorded in several high dose animals. Microscopically, minor liver hypertrophy was seen in some high dose animals but reported as less obvious than in the 13 weeks treated group.

In the 6-months study in **dogs** where 0.4, 1.5 and 8mg/kg melatonin were used, increased serum glucose levels were observed at some time points of the study. Microscopic examination revealed pituitary gland and parathyroid cysts, adenomyosis of the uterus, capsular fibrosiderosis of the spleen and cytoplasmatic rarefaction of hepatocytes consistent with the presence of glycogen. Based on toxicokinetic data the Cmax values obtained with the mid and high doses were high in excess to the levels to be reached in man under therapeutics.

- Genotoxicity

The full battery of genotoxicity tests according to ICH standard have been performed. The Ames test, *in vitro* gene mutations in mouse lymphoma cells, *in vitro* chromosome aberration in human lymphocytes and *in vivo* mouse micronucleus were all negative.

Additional data from the literature investigating the mutagenic potential of melatonin and 6-hydroxymelatonin using a reduced Ames test (three strains of *Salmonella typhimurium*) concluded also that both molecules were not mutagenic (Neville et al, 1989, *Journal of Pineal Research, 6:73-76*). Further literature data report that melatonin and two related compounds, 6-hydroxymelatonin, the principal metabolite of melatonin, and 5-methoxyindoleacetric acid (5-MIAA) were screened for relevant information associating these chemicals with respect to mutagenic or carcinogenic effects (DEREK system). No structural alerts were identified.

Overall, it is concluded that melatonin does not present any genotoxic potential.

- Carcinogenicity

The carcinogenic potential of melatonin was evaluated in one long-term rat study and a short term mouse study (US, NTP study)
In the combined rat chronic toxicity and oncogenicity study (104 weeks), an increased incidence of pituitary adenomas in high dose males was reported with statistical significance at $p<0.036$. Since this type of tumour is classified as common in the rat, the statistical significance is below the value of triggering concern ($p<0.01$).
In addition, thyroid tumors were observed at the higher doses in rats and the CHMP requested a mechanism explanation.

Table: Incidence of thyroid neoplastic and non-neoplastic lesions in the 104 rat carcinogenicity

	Male		Female	
	Neoplastic[a]	**Non-neoplastic[b]**	**Neoplastic[a]**	**Non-neoplastic[b]**
Control	15/100 (15.0%)	10/100 (10%)	11/99 (11.1%)	2/99 (2%)
15 mg/kr	5/17 (29.4%)	3/17 (17.6%)	5/22 (22.7%)	0/22 (0%)
75 mg/kg	8/29 (27.6%)	12/29 (41.4%)	2/29 (6.9%)	13/29 (44.8%)
150 mg.kg	13/50 (26.0%)	21/50 (42%)	4/50 (8.0%)	14/50 (28%)

[a] B-C-cell adenomas + all thyroid carcinomas

[b] B-follicular cell hypertrophy

Liver enzyme induction was suggested as the possible mechanism but no supportive data had been provided. The applicant has been requested to provide animal data on hepatic and thyroid findings that might allow a mechanistic association in both organs.

An increased incidence of thyroid macroscopic and microscopic findings in treated animals when compared to the controls was apparent but not clearly correlated with liver findings.
The effect of melatonin on liver enzymes as discussed by the applicant, based on data collected from studies with human material as well as from published animal studies, suggest that thyroid hormone metabolism by the CYP enzyme family is not probable.

However, since melatonin has been shown in two rat studies (newly presented) to increase the levels of enzymes involved in thyroxin conjugation (glutathione S-transferase activity and glucuronyl transferase), this could result in increased elimination leading to increased TSH by feed back mechanism, with the consequent increased thyroid cell proliferation. Therefore, based on this additional information provided, the proposed mechanism for increased thyroid tumorigenesis appears reinforced but not proven, since data from direct measurements of thyroxin as well as TSH in melatonin treated animals has not been provided. The applicant committed to provide these data in post-authorisation as a follow-up measure.

A short-term carcinogenicity study in transgenic animals on the behalf of US-NTP, published in 2000 (Rao et al, 2000, *Breast Cancer Research and Treatment*, 64:287) was also provided.
The study was performed in hemizygous TG.NK female mice with MMTV/c-neu oncogene. The melatonin treated groups received 50-200mg/kg melatonin or melatonin 50mg/kg combined with 0.10ml flaxseed oil. Melatonin did not show any tumorigenic potential in this model.

- Reproductive Toxicity

The reproductive toxicity profile of melatonin has been characterised through Applicant sponsored studies and published studies (US National Toxicity Programme (NTP))

Fertility and early embryonic development in the rat.
24 animals/sex/dose were treated orally by gavage with 0, 15, 55 or 200 mg/kg/day of melatonin. There were no reports of effects on embryo-foetal development following the treatment of the pre-mated rats at the doses used. The mean incidence of pre-implantation loss in the high dose group (15%) was greater than that of concurrent controls (7.5%) and outside the recent background control range (8.7% to 14.5%) but the values did not show statistical difference. Post-implantation loss was not affected by the treatment. The oestrous cycle, mating performance and fertility were not changed by treatment. Also the sperm number, motility and morphology were unaffected by the treatment.
It is known from the literature, that in many mammals, melatonin controls the reproductive cycle. Melatonin influences the levels of LH and FSH across many species. In women it can inhibit ovulation (Voordouw, 1992, *J.Clin Endocrinol and Metab; 74(1):108*).

Embryo-foetal development

Rat Developmental Toxicity
In a NTP rat study, melatonin was administered by gavage to 25 timed-mated CD® female rats on gestation day 6 to 19, at doses of 50, 100 and 200 mg/kg/day.

No maternal deaths were observed and the clinical signs reported were classified as minimal. Transient reduction of the body weight gain and relative decreased food intake were observed at the high dose group. Increased relative maternal liver weight was also observed in the animals from mid and high dose. Absolute liver and gravid uterine weights were not affected. The endpoints related to embryo/foetal growth, viability or morphological development were not modified by melatonin treatment. Based on the lack of embryo/foetal toxicity, the developmental toxicity NOAEL of melatonin was considered as 200 mg/kg/day. Based on the slight maternal toxicity reported at 200 mg/kg/day treated animals, the maternal toxicity NOAEL was considered as 100 mg/Kg/day.

Rabbit Developmental Toxicity
A study of the embryo-foetal development in the NZW rabbit was performed by the applicant with oral administration of melatonin at 0 (control), 15, 50 and 150 mg/kg/day from days 7 to 19 of gestation.

There were no dose-related maternal effects at any dose. No effects were observed on pre or post-implantation loss and mean number of foetuses/female. Foetal, litter and placental weighs were not affected by treatment. Visceral and skeletal malformations and/or variations were observed in all groups including controls. Some of such malformations/variations showed a trend or a significant increase in the treated groups, such as absence of lung or iliac alignment/caudal shift of vertebrae at high dose corresponding to an approximate AUC of 24000 to 45000 ng.h/ml. When compared to the AUC values to be achieved in man (<4 ng.h/ml), very high exposure ratios were reached in this study.

An abundant literature can also be found, addressing the effects of melatonin in the reproductive function, using oral or sc route in several species, many of them in seasonal breeders or in cattle where melatonin is used to influence the reproductive process through a control of the oestrus cycle.

Pre-and postnatal developmental study in rats
24 pre-mated females were treated with 0, 15, 55 and 200 mg/kg/day of melatonin from Day 6 of gestation to Day 21 post-partum, inclusive.
The treatment had no effect on parturition and outcome of pregnancy but the subsequent growth and viability of the high dose offspring was slightly reduced during lactation.
At weaning, a slight reduction of offspring maturity was observed in all dose groups, but the subsequent F1 development was not modified. Therefore, melatonin intake during lactation is to be avoided. This is reflected in the SPC (section 4.6).

- Toxicokinetic data

Repeat-dose toxicity

Toxicokinetic parameters in rats

Table: Toxicokinetic parameters for melatonin derived from composite plasma profiles at days 1 and 7.

Dose mg/kg/day	Sex	C_{max} ng/ml		$AUC_{(20\text{-}t)}$ ng.h/ml	
		D1	D7	D1	D7
15	M	2154.1	1269.5	95090	43910
75	M	11963	7399.9	1027265	454868

150	M	20316	11382	2568891	1159593
15	F	1242.7	1637.6	53612	40182
75	F	14508	9628.7	1268844	720418
150	F	24931	19608	2458843	1918896

The values of AUC increased more than proportionally to the dose and after repeated exposure the values were reduced as compared to those at day 1. The plasma concentrations measured along the study decreased along the exposure time. No further AUC values were determined. The animals systemic exposures along the study are therefore not evaluable and appropriate exposure ratios *vs* man cannot be calculated. The $AUC0_{-24h}$ after 2 mg melatonin in human is 3846 pg.h/ml.

Toxicokinetic parameters in dog

Table: AUC vs time (ng.h.ml)

Dose (mg/Kg)	Day 1	Day 85	Day 175
0	--	0.469±0.238	0.072±0.01
0.4	14±8	15±7	21±10
1.5	128±48	178±47	183±82
8.0	1493±544	3819±883	3424±905

Table: Values of C_{max} (ng/ml)

Dose (mg/Kg)	Day 1	Day 85	Day 175
0	--	--	--
0.4	27±17	16±4	33±15
1.5	186±127	313±66	286±130
8.0	2600±1269	3239±1046	4614±932

The AUC and Cmax values increased with dose in a non-linear manner (more than proportional). There was no relevant time or sex difference in dogs.

- Local tolerance

No specific studies were performed, which is acceptable considering the oral route of administration and the absence of gastro-intestinal findings in the general toxicology studies.

Ecotoxicity/environmental risk assessment

The initial environmental risk assessment included only a calculation of $PEC_{surface\ water}$ which was wrong (0.00002µg/l instead of 0.00002mg/l for an intended maximum daily dose of 4 mg). The correct value is above the trigger value of 0.01µg/l and therefore phase II studies are in principle needed. The applicant was requested to discuss the need for such studies.

The re-calculated the PEC surface water on the basis of the new posology (2mg/day) and the administration schedule proposed (3 weeks followed by 2 months interval, resulting in 15 weeks of exposure), resulted in a value below the trigger limit. Therefore further phase II studies were not requested by the CHMP considering that Circadin, at the recommended posology, did not present any potential risk to the environment.

Discussion on the non-clinical aspects

While the current understanding of endogenous melatonin is substantial, especially regarding melatonin's involvement in the circadian timing system, its putative role in regulating sleep and how this role is mediated remains unclear. *In vitro*, melatonin is described in the literature as acting at the

central nervous system level, modulating the synchronisation of the biological clock and promoting sleep through stabilisation and phase-shifting effects on the suprachiasmatic nucleus of the hypothalamus possibly involving interaction with melatonin MT1 and MT2 receptor subtypes. *In vivo*, studies in animal looked essentially at sleep induction effects, but the results are difficult to interpret and extrapolate to humans.

The mean oral bioavailability varies from 17% to 100 % depending on the dose and the animal species. Melatonin is promptly distributed in tissues and rapidly metabolised in the liver mainly by CYP1A enzymes. The main excretion route is renal accounting to 60-70% of the dose in the rat excreted as sulfo-conjugates (70-80% of excreted fraction) or gluco-conjugates (5%).
Melatonin has a low toxicity after single administration. In repeat-dose toxicity (rats and dog) effects on the liver (hypertrophy) and genital tract of male rats and female dogs were observe at exposure in large excess of the intended human exposure at therapeutic dose.
In reproductive studies, melatonin induced some toxicological effects on the embryo-foetal development in rabbits and on the postnatal developmental in rats. Therefore, the use of Circadin is not recommended during pregnancy and lactation. This is reflected in sections 4.6 and 5.3 of the SPC.

The carcinogenic potential, has not been completely elucidated in view of the thyroid findings in the rat carcinogenicity study and further mechanistic data will be provided as a post-authorisation commitment. Since no genotoxic properties have been identified for melatonin, and as the animal exposure was in large excess to the expected one in the clinic, considering also that the treatment is not proposed to be continuous for long periods, and provided that this well established mechanism of thyroid tumorigenesis in rodents can be clearly proven by the applicant (follow-up measure), the risk to humans appears to be minimal.
Overall, the non-clinical safety profile of melatonin appears acceptable for the proposed short-term indication (one 2mg tablet/day for 3 weeks).

3. Clinical aspects

Introduction

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

An oral prolonged-release formulation of melatonin (Circadin. 2 mg Tablets) was developed, in order to circumvent the fast clearance of the hormone and to provide a melatonin profile in the blood more closely matched to the normal physiological profile.

Dissolution profiles have been used to select the most appropriate formulation, to establish the slow release character of the formulation, to ascertain similarity on batches produced in different manufacturing sites and to establish a linear *in vitro-in vivo* correlation (level A). In order to establish profile similarity, F2 values for 32 comparative dissolution profiles involving different batches of melatonin tablets were provided in accordance with the Note for Guidance on bioavailability and bioequivalence. The results show that at each of the three pH conditions, all comparisons had an F2 value of greater than 50, indicating that the different sources of tablets resulted in similar in vitro dissolution data.

The pharmacokinetic profile of Circadin 2 mg was studied in 3 specific studies in healthy volunteers. In one, an interaction with food was explored. In addition, a comprehensive review of the extensive literature published on melatonin pharmacokinetics has been provided.

In one of the studies (Kitzes et al), the pharmacokinetics of a single dose of Circadin 2mg, prolonged release was investigated in a three way study in 8 healthy male volunteers.
The study was divided in 3 parts: basal- in the first 24 h beginning at 10:00 am and ending at 10:00 am after 24h. The basal levels of melatonin in blood and 6- MTS excretion in urine were measured. In the second phase Melatonin 2 mg were administered at 10:00 am without food and the same measurements were done. In the third phase Melatonin 2mg was administered at 10:00 am with a standard meal.

The circadian rhythm of plasma levels of endogenous melatonin is clear from the analysis of basal plasma levels during an entire 24 h period. Cmax is reached ca. 18 hours after the start of the study (ca. 4 o'clock pm). Comparison of plasma levels following administration of 2 mg melatonin with basal levels gives a 6 fold difference in AUC and 8 fold difference in Cmax
However, because of the design of the study (no cross-over) and the small number of subjects, it is not possible to draw firm conclusions on the food effect, subject variability and period effects in this study.

The results are summarised in the table below:

Table: Melatonin pharmacokinetic parameters, 2 mg melatonin, prolonged release

	AUC 0-24h (pg.h/ml)	Cmax (pg/ml)	Tmax (hours)	Plateau time (h)
Basal state				
Mean ± sd	448±288	58±32	18.5±2.1	6.9±1.7
Median	375	51	18	6.6
Range	150-1017	30-126	16-22	4.7-9.6
Drug fasting				
Mean ± sd	2527±1200	427±211	1.6±0.8	5.1±2.3
Median	2257	393	1.5	4.4
Range	823-4478	180-855	0.5-3	3.1-9.9
Drug with meal				
Mean ± sd	2405±1469	483±253	2.6±1.1	3.5±1.4
Median	2010	390	2.5	3.1
Range	618-5252	205-1020	1-4	1.7-5-5

The rate and extent of urinary excretion of melatonin's main metabolite (6-sulphametoxymelatonin) has been measured as well:

MT 6-S pharmacokinetic parameters

	Daily excretion (mg/24h)	Maximal excretion (μg/h)	Time of max.excretion (h)
Basal state			
Mean ± sd	0.03±0.02	4.5±2.7	19.3±0.7
Range	0.01-0.05	2.1-10.6	19-21
Drug fasting			
Mean ± sd	3.2±0.7	737±233	2.8±1.3
Range	2.5-4.7	526-1318	1-5
Drug with meal			
Mean ± sd	2.9±0.7	743-251	4.3±1
Range	1.8-3.9	526-1318	3-5

Analytical methods
The measurement of plasmatic melatonin and of the metabolite 6-SMT used a radioimmunoassay and an ELISA method for 6-SMT in the urine. Although the validation reports are not entirely satisfactory, the CHMP considered that the studies have been performed under acceptable conditions.

- Absorption

The absorption and bioavailability of orally administered melatonin in humans has been extensively reported in the literature. Low oral bioavailability has repeatedly been shown, typically in the range 10-20%, and is associated with high inter-individual variability due to extensive first-pass metabolism.

Although there seems to be considerable variability, the absolute bioavailability of melatonin appears to range from 10 to 56% with figures of 15% and 30% reported by other studies at doses less than or equal to 4 mg. At higher doses, some of the reported data reveals inconsistencies, and high variability.
Published data shows that melatonin has a short half-life in animals and humans. Peak plasma levels are reached 20-30 minutes after oral administration and are maintained for approximately 90 minutes. The plasma elimination $t_{1/2}$ in humans is around 40-50 minutes.

The applicant performed three studies covering food effects, comparison with an oral solution, dose proportionality and gender effects.
In one of the studies, the pharmacokinetics of Circadin 2 mg was compared under both fasting and non-fasting conditions to a 2 mg solution of melatonin. The participants were healthy male and female volunteers, aged between 55 and 69 years of age.

The bioavailability of the solution under fed conditions, as expressed by the relative fed/fasted AUCI, was slightly higher than the corresponding fasted administration: 109.0% (90% confidence interval 87.6- 135.7%).

Following Circadin 2 mg oral administration T_{max} occurs after 3.0 hours in a fed state. Food reduced the peak plasma concentration of melatonin from the tablet and solution formulations by approximately 13% and 50% respectively with no apparent difference in the rate of absorption in both adults older than 55 years and in younger volunteers. Food also delayed the time to the peak plasma concentration by a median difference of 2.25 hours from the tablet formulation, but not from the solution.

- Distribution

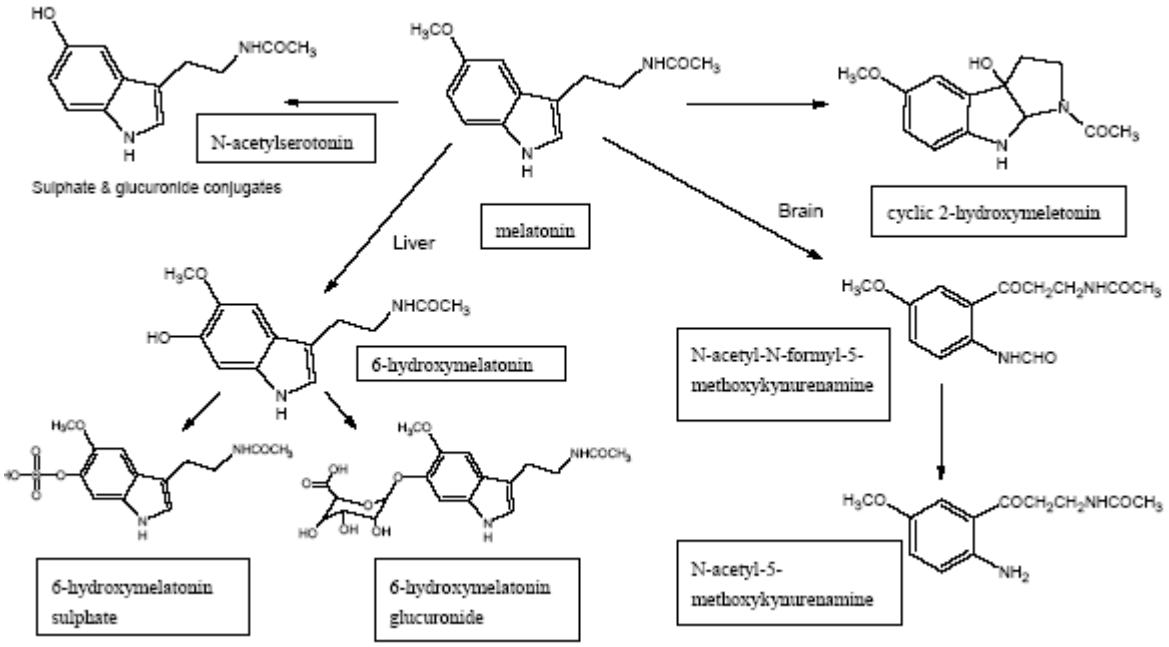
The *in vitro* plasma protein binding of melatonin is 61.2%. Circadin is mainly bound to albumin, alpha1- acid glycoprotein and high density lipoprotein. The binding to the other serum proteins is insignificant. The melatonin binding was constant over the range of the studied concentrations in serum. Literature data indicates that melatonin is distributed in all body fluids and is accessible at all tissues. The mean binding of melatonin to erythrocytes is 49.0%.

Melatonin is not strongly or extensively bound to plasma proteins, therefore protein binding effects on pharmacokinetics are not expected to be significant.

- Metabolism and Elimination

The literature reviewed by the applicant provides information regarding the metabolic fate of melatonin. Melatonin is 90% metabolised in the liver involving mainly CYP1A1 and CYP1A2 (while CYP2C9 andCYP2C19 are assumed to be less important) yielding 6-hydroxymelatonin whose sulphate conjugate (6-sulphatoxy melatonin) accounts for 80% of the dose excreted in the urine. The other main metabolite results from melatonin O-demethylation, yielding N-acteylserotonin. No figures are provided as to the extent of urine excretion of the secondary metabolite, mainly the glucuronide conjugate of 6-hydroxymelatonin. From one of the studies reviewed, it appears that repeated dose administration does not alter the metabolic profile of melatonin.

Figure 1 Melatonin Metabolic Pathways



- Dose proportionality and time dependencies

No conclusion regarding dose proportionality can be firmly drawn. Three doses have been studied (1 mg, 4 mg and 8 mg). The 1 mg dose was obtained by halving one 2 mg tablet. This introduces uncontrollable factors (dose inaccuracy, interference with the matrix releasing mechanism) that make the results obtained with this dose unreliable. The 4 mg and 8 mg doses appear to be proportional, but with only 2 points the results are inconclusive.

Therefore since the safety at the higher doses and the proportionality between the recommended dose (2 mg) and the higher doses of 4 mg and 8 mg have not been established, the applicant decided to remove from the SPC the claim to use doses higher than 2 mg.

- Special populations

Impaired renal function

A study on patients with end stage renal disease under chronic haemodialysis showed that melatonin plasma concentrations were comparable to the ones from healthy subjects. However, other stages of renal insufficiency not compensated with haemodialysis have not been studied. Therefore there is no evidence that renal insufficiency does not affect melatonin elimination. Consequently, it is recommended in the SPC that caution should be used when melatonin is administered to such patients.

Impaired hepatic function

In the literature, one study examined plasma melatonin levels in patients with cirrhosis and subclinical hepatic encephalopathy and found an abnormal plasma melatonin pattern in these patients compared with healthy controls. In the hepatically impaired, the onset of the increase in plasma melatonin levels and the melatonin peak during the night were both displaced to later hours. Furthermore, plasma melatonin levels in patients with cirrhosis were significantly increased during daylight hours. In a later study, the same authors measured nocturnal urinary 6-sulphatoxymelatonin excretion in 21 hospitalized cirrhotic patients with normal renal function. The cirrhotic patients had a significantly decreased total excretion of 6- sulphatoxymelatonin compared with controls (median value of 8.28 µg, (range 0.85 to 28.1 µg) compared to 12.21 µg (range 9.12 to 29.04 µg; $P < 0.05$). Because of the existing elevated melatonin levels, it is believed that patients with hepatic impairment are unlikely to benefit from therapy with oral melatonin. Therefore, it is mentioned in the SPC that Circadin is not recommended for use in patients with hepatic impairment.

Gender, smoking and age
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. No pharmacodynamic differences between males and females were found despite differences in blood levels.
CYP 1A2 isozyme can be induced by smoking and therefore decrease melatonin levels. This is mentioned in the SPC.

- Pharmacokinetic interaction studies

There are 4 studies conducted by Neurim pharmaceuticals to elucidate potential drug interactions with Circadin, namely with zolpidem, cimetidine, thioridazine and imipramine.
Interaction studies between Circadin and zolpidem showed an expected transitory pharmacodynamic effect one hour following concomitant administration, resulting in increased impairment of attention, memory and co-ordination compared to zolpidem alone.

PK drug/drug interactions have been found with 5- or 8-methoxypsoralen, caffeine, cigarette smoking, testosterone and oestrogen.
Melatonin metabolism is mainly mediated by CYP1A2, a Cytochrome P450 isozyme known to be inhibited by fluvoxamine, ciprofloxacin and other quinolones, and induced by several drugs (e.g. caffeine, carbamazepine, omeprazole) and cigarette smoking. CYP1A2 substrates such as theophylline and clozapine may also give rise to interactions.

Inhibition and induction potential of melatonin on CYP450 enzymes has been studied *in vitro* at the request of CHMP.
The main CYP450 enzymes (CYP1A, 2C9, 2C19, 2D6, and 3A) have been studied. The results show that CYP1A is the main CYP enzyme inhibited by melatonin with 48% inhibition from control. This is in agreement with published literature. Induction studies indicate that both CYP1A and CYP3A (and consequently CYP2C) enzymes are not induced by melatonin.
Concerning adrenergic agonists/antagonists, opiate agonists/antagonists, anti-depressant drugs, prostaglandin inhibitors, benzodiazepines, tryptophan and alcohol, data in the literature regarding their effect on endogenous melatonin levels show that these active substances affect the endogenous secretion of melatonin in the pineal gland but not its metabolism.

The SPC section on drug/drug interactions adequately reflect the findings in the literature and from studies performed by the applicant

Pharmacodynamics

- Mechanism of action

The applicant did not conduct any studies specifically aimed at elucidating the mechanism of action of melatonin. There is a huge body of scientific studies that pretend to clarify some aspect of the mechanism of action of melatonin. However these studies are heterogeneous in the formulation and doses used and at present, the mechanism of action of melatonin, most likely multi-factorial, still remains unknown.

The mechanism by which melatonin produces sleepiness in humans is unclear. Evidence suggests that exogenous melatonin has a short half-life and it penetrates the blood-brain-barrier.

The hypnotic effect of melatonin might be related with:

a) Thermoregulatory mechanisms – by lowering core body temperature melatonin may reduce arousal and increase sleep-propensity;

b) Modification of brain levels of monoamine neurotransmitters. It is known that melatonin and its analogues do not interact with benzodiazepines or cannabinoid receptors;

c) Modification of the phase of circadian rhythm;

d) Opposite effects on GABA-A receptors in specific brain areas: GABA-A receptors in suprachiasmatic nucleus are potentiated via MeIIa receptors, while they are inhibited in the hypothalamus via MeIIb receptors.

- Primary and Secondary pharmacology

Melatonin (N-acetyl-5-methoxytryptamine) is the major hormone produced by the pineal gland. The concentration of the hormone in blood is increased during the hours of darkness, while a low concentration occurs during the day. Because of its possible role in influencing the circadian rhythm of sleep, melatonin has been used for treating sleep disorders.
Melatonin is metabolised to 6-hydroxy-melatonin in the liver and the main metabolite excreted is 6-sulphatoxy-melatonin. Isolated measurements of melatonin are difficult to interpret given its circadian secretion, however urinary excretion of 6-sulphatoxy-melatonin may be helpful in studying pineal function.

The therapeutic exploratory studies described later in this document contribute to the availability of data on sleep effects.

Clinical efficacy

Following the withdrawal of the first MAA for Circadin (see Introduction), the Applicant has submitted a new MAA package that includes all the data that were submitted in the first MAA and additional data extracted from the new studies performed during 2003-2005.

Three additional studies, performed during the period 2002-2005 were submitted. These studies appear under the code names NEURIM-VIIIa, NEURIM-VIII & NEURIM-IX.
NEURIM-IX is included in order to support the efficacy of Circadin, for the indication of "treatment of poor quality of sleep in patients suffering from primary insomnia".

NEURIM-VIIIa, has been performed in order to demonstrate "assay sensitivity of the used assessment tools in the pivotal studies through the use of an active comparator hypnotic".
Finally NEURIM-VIII was discontinued, due to non-optimal rate of enrollment of patients. Therefore the data from this study are being used only to enrich the safety database of the compound.

The data package includes the following new items:

Efficacy Study		
Neurim-IX	To determine the efficacy and safety of 2 mg Circadin once daily in patients >55 years old with insomnia for 3 weeks treatment. Double blind placebo controlled, randomized two arms study	PR: 2 mg and placebo in DB phase
Special Populations and a Safety Studies		
NEU951005a	To determine the efficacy and safety of Circadin once daily in diabetic patients suffering from insomnia Double blind, placebo-controlled, randomized cross-over	PR: 2 mg or placebo
NEU BP	To determine the efficacy and safety of Circadin once daily in patients with nocturnal hypertension (n=38)	PR: 2 mg or placebo
NEU201005	To determine the efficacy and safety of Circadin once daily in patients with end stage renal disease	PR: 2 mg or placebo

Neurim-VIII	To determine the efficacy and safety of 2 mg Circadin once daily in patients > 55 years old with insomnia for 3 weeks treatment. Double blind placebo controlled, randomized two arms study (discontinued due to problems in patients recruitment)	PR: 2 mg and placebo in DB phase.
External Comparator Study - Methodology Validation		
Neurim VIIIa	To determine the efficacy and safety of 10 mg zolpidem once daily in patients > 55 years old with placebo controlled, randomized two arms study.	Zolpidem 10 mg and placebo in DB phase.

- Exploratory studies

The applicant conducted 5 small, short duration studies as exploratory trials with the aim of validating trial methodology and a sleep laboratory study (Neurim I). This last study is also considered by the applicant, to be a phase III pivotal study.

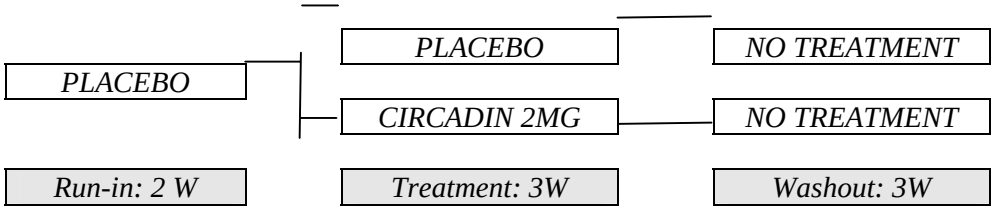
Table: Early Investigational and Pilot Studies

Study No. Location	Study Design	Subjects	Inclusion	Dosage /Duration
Study No 1 Israel	DB, PC, R, three-way CO	Three groups: 8 (4M, 4F), ave. age: 73; 18 (6M, 12F) avg. age: 81 25 (19M, 6F) ave. age 71	independent insomniacs institutionalised insomniacs; elderly non-insomniacs	CR, FR:2 mg/day (one week)
Study No. 2 Israel	PC, SB	14 patients Sex/age not stated	Probable Alzheimer's disease with reported sleep disturbances	2 mg/day (one week)
Study No. 3 Israel	SB, comparison between CR and FR	51 patients Age/sex not stated	Healthy volunteers suffering from Delayed Sleep Phase Syndrome (DSPS)	CR: ½, 1, 2 mg/day FR: 1, 2 mg/day
Study No. 4 Israel	DB,,, PC, R	10 (M)	Healthy volunteers	CR 2mg/day, FR ½, 1, 2 mg/day (3 days)
Study No 5 Israel	DB, PC, CO	12, Aged 76 (SD 8) years	elderly subjects complaining of insomnia	CR:2 mg/day (3 weeks), One week washout
NEU30424 The Netherlands	MC, PC, R, two period CO	N = 26 enrolled, 18 randomised; 16 completed. 55-85 years,	Elderly patients with insomnia and melatonin deficiency	Circadin 2 mg/day One week placebo run in. Period 1, 4 week treatment period. After 1 week washout, 4 week Treatment Period 2.

DB-Double-blind, SB- single blind, PC-placebo controlled, R – randomised, CO- crossover.
CR – Controlled release, FR - fast release

Neurim I – sleep inducing and maintaining efficacy of Circadin in elderly insomniacs, a double-blind, placebo controlled, parallel group sleep laboratory study.

This is a double-blind (DB), placebo controlled (PC), parallel group design (PGD), sleep laboratory study. The study has 2 phases: 2 weeks run-in, 3 weeks DB, PC, PGD and 3 weeks withdrawal period. According with the following schema:



The patients enrolled were male or female over 55 years of age suffering from primary insomnia according with the DSM-IV criteria. They were otherwise healthy.

The primary variable was a polysomnography parameter - the Total Duration of Awakenings After Sleep Onset (DWASO).

As secondary objectives: Circadin versus placebo was compared in all other hypnographic variables, in all night spectral EEG, actimetric parameters and sleep/wake quality questionnaires plus in diurnal psychomotor and neurocognitive tasks. The effects of wash-out in all of the mentioned tests (they were measured at two occasions- early withdrawal and late withdrawal ; safety evaluation.
The sample size was 40 patients (20/group).

Results:
1. Polysomnographic variables
The results on the primary outcome of this study – DWASO – showed no difference with placebo.

Secondary outcomes:

At end of treatment, an effect of Circadin is shown over some sleep induction polysomnographic variables: sleep onset latency (SL) was shortened by 9 min on average (p=0.011), duration of wake prior sleep onset (DWAPSO) and DWAPSO as % of Time spent asleep (TSA) [DWAPSOP] are decreased by about 50% under Circadin in comparison to placebo or intra-group baseline values (p=0.011 and p=0.02 respectively).

No difference between Circadin and placebo were found in a number of other polysomnographic variables:

- sleep maintenance variables: number of awakenings prior to sleep onset-WASO,
- sleep efficiency – SEF,
- number of stage shifts – STSH
- variables assessing sleep induction and sleep maintenance at early and late withdrawal

2. Other secondary variables

There was no difference between groups for the duration of the different sleep stages, all night spectral EEG, actimetric parameters (Somnitor) and sleep/wake quality questionnaires.

Sleep diaries showed that 20% of the Circadin group exhibit advanced phase that reverted during the withdrawal period. The difference of this parameter to placebo is statistically significant. Significant treatment effects for the Critical Flicker fusion test under Circadin vs. placebo were observed at the end of treatment and late withdrawal. There is also a significant treatment effect for the Total reaction time in all steps of the trial.

In conclusion, the primary variable in this trial failed to reach significance. An effect of Circadin over sleep induction parameters is present during the treatment phase and they revert to close to baseline during withdrawal. The effect size is around 50%. However this is an exploratory trial, with small sample size and it is based on polysomnographic evaluation. It is then just a hypothesis generating study.

- Dose response studies

The clinical development program contains two dose ranging studies (Neurim IV and Neurim V) with one long-term open-label safety follow-up (Neurim V). The primary measure of efficacy in the dose - ranging and long-term safety was based on quality of sleep derived from the Leeds Sleep Evaluation Questionnaire (LSEQ).

Neurim V (982001) France, Israel	Dose ranging. Evaluate safety and efficacy of Circadin 1 mg, 2 mg and 5 mg compared to placebo based on the QOS variables of the LSEQ	Multi-centre, randomised, double-blind, placebo controlled, dose ranging, parallel group. Long term (12 month) open lable extention with Circadin 2 mg.	Randomised: 263 ITT: 257 PP: 214 Adult insomniac patients according to DSM-IV criteria, aged ≥20 years to ≥80 years.	Test: Circadin 1 mg, 2 mg and 5 mg Tablets Control: Placebo matching Circadin 6 week DB, followed by long term (up to 52 weeks) open label treatment with Circadin 2 mg.
Neurim IV France	Dose ranging. Evaluate safety and efficacy of Circadin 0.2 mg, 0.5 mg, 2 mg and 5 mg compared to placebo based on the QOS variables of the LSEQ.	Multi-centre, randomised, double-blind, placebo controlled, dose ranging, parallel group.	Randomised: 393 ITT: 393 PP: 316 Insomniac patients according to DSM-IV criteria, aged ≥55 years.	Test: Circadin 0.2 mg, 0.5 mg, 2 mg and 5 mg Tablets. Control: Placebo matching Circadin

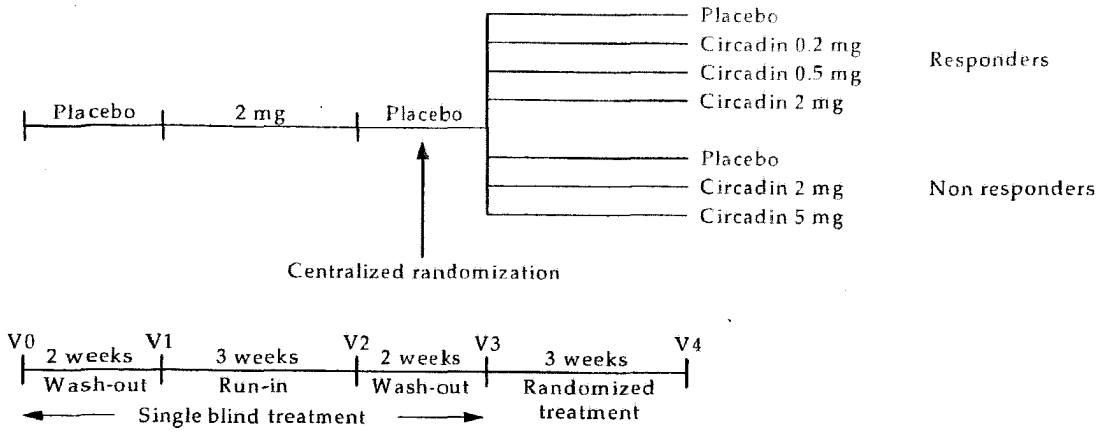
The Leeds Sleep Evaluation Questionnaire (LSEQ) is a widely used standardized instrument for the measurement of sleep difficulties in clinical settings and like other standardized questionnaires for the same purpose consists of several well defined components (Hindmarch and Parrott, 1978). It comprises ten individual visual analogue scales (100mm) which have been shown by factor analysis to assess four discrete, independent domains of sleep and daytime behaviour: Getting To Sleep (Questions 1-3) Quality Of Sleep (Questions 4,5) Awakening From Sleep (Questions 7,8) and Behaviour Following Wakening (Questions 8-10). (Parrott and Hindmarch, 1980).

Thus, the mean of questions four and five was used as an independent measure of Quality of Sleep and equally questions 8-10 of Behaviour Following Wakening as a measure of functioning the following day.

Neurim IV – A double-blind, parallel groups, randomised, placebo-controlled, dose ranging study of the effects of Circadin in insomniacs over 55 years of age, in responders and non-responders to the single-blind administration of 2 mg Circadin.

The aims of this trial were: to identify responders and non responders to Circadin 2mg using clinical criteria; to determine the smallest effective dose in the responders group; to test whether the non-responders could benefit from lengthening the treatment period or by increasing the dose to 5 mg.

The population were patients > 55 years old with primary insomnia. The study comprised 4 periods: periods 1 and 3 were single blind placebo treatment periods, period 2 was a single blind Circadin period, and period 4 was a randomised DB, PC, PGD. Period 1 and 2 were used to allocate responders and non-responders based on the improvement of 20% in Quality of sleep in the Leeds sleep Questionnaire record at Visit 1 (placebo) versus visit 2 (Circadin 2 mg) The second placebo period was used as a pre-randomisation baseline step. During period 4 responders randomly received either 0,2, 0,5 or 2 mg/d of Circadin or placebo; non-responders randomly received either 2 or 5 mg/d of Circadin or placebo. A diagram of the design is presented below:



The evaluation of efficacy was based upon the following assessments:

Leeds questionnaire

- Average score of each of the 4 combined variables (Quality of Sleep-QOS, Getting to sleep-GTS, Awakening from sleep-AFS, behaviour following wakefulness-BFW);
- Actimetric variables: sleep efficiency, sleep latency, total sleep time, time awake after sleep onset, number of awakenings;
- Sleep log (for the 7 days before visits V1, V2, V3 and V4): % of nights with a score of "very good" or "good"; % of days with a score of "very good" or "good"; average number of hours of sleep; average number of awakenings; average sleep efficiency; average duration of wake after sleep onset; average latency.

The primary variable for the evaluation of efficacy is the change between visits 3 and 4 of the quality of sleep (QOS) The other secondary variables are all the other parameters derived from the Leeds questionnaire, actimetric and sleep log between visit 3 and 4

Intention-to-treat (ITT) population is the 393 randomised responders and non responders. Among these patients, 228 were responders and 165 were non responders. The primary efficacy analysis was conducted on a per protocol (PP) basis after a pre-specified protocol amendment.

Results

The detailed results are complex because they involved many parameters and several trial phases. The key points are the following:

1. The single blind treatment period with Circadin 2 mg in-between placebo treatment periods was aimed to differentiate responders from non responders on the basis of an improvement of 20% in Quality of Life score- Leeds questionnaire. In the end of this Circadin single blind period there was a statistical significant difference relative to the status at the beginning of that period (V1) in all clinical sleep parameters and in the two sleep log variables. According with the criteria 57% of the treatment completers were classified as responders and the 43% as non-responders.

2. After this single blind treatment period with Circadin both responders and non-responders were entered in a placebo period in order to bring their status to the baseline pre-treatment one. However, a return to the baseline values did not occur. At the end of the second placebo period when randomisation for the dose-finding period was due, the population was significantly better then at entry in study. Carry-over effect from the Circadin single-blind period was present.

3. The patients were anyhow randomised. Responders to the following doses: 0.2, 0.5, 2 mg or placebo. Non-responders to 2, 5 mg or placebo. It should be remembered that the primary variable established in the protocol was Quality of sleep in the randomised phase of the trial. The table below summarises the actual data in this variable.

Primary efficacy endpoint: Quality of Sleep (QOS) as quoted with the Leeds Questionnaire (tables 14.2.C.1)

Dose	V3 Mean (sd)	V4 Mean (sd)	V4 - V3 Mean (sd)	95% CI	Results of Ordered Tests (t-test)
Quality of Sleep					
Placebo	39.8 (21.0)	36.5 (20.5)	-3.3 (23.8)	[-10.3; 3.7]	
0.2 mg dose	43.3 (21.1)	38.0 (15.2)	-5.3 (17.5)	[-11.0; 0.4]	NA
0.5 mg dose	39.9 (13.7)	34.5 (17.8)	-5.4 (14.8)	[-9.7; -1.1]	NA
2 mg dose	38.4 (17.8)	33.0 (16.3)	-5.5 (14.8)	[-9.8; -1.1]	p = 0.599

Other variables derived from the Leeds questionnaire (tables 14.2.C.1):

Dose	V3 Mean (sd)	V4 Mean (sd)	V4 - V3 Mean (sd)	95% CI	Results of Ordered Tests (t-test)
Getting to Sleep					
Placebo	42.1 (15.2)	36.8 (17.1)	-6.6 (15.1)	[-11.1;-2.0]	
0.2 mg dose	42.4 (14.4)	38.2 (14.4)	-4.3 (15.3)	[-9.2; 0.7]	NA
0.5 mg dose	43.3 (14.4)	38.5 (16.0)	-4.0 (11.6)	[-7.4; -0.6]	NA
2 mg dose	42.6 (15.6)	37.5 (15.8)	-5.4 (12.3)	[-9.0; -1.7]	p = 0.684
Awakening from Sleep					
Placebo	39.9 (17.2)	36.7 (19.2)	-3.9 (14.9)	[-8.4; 0.6]	
0.2 mg dose	40.9 (16.2)	35.8 (16.0)	-5.1 (17.6)	[-10.8; 0.6]	NA
0.5 mg dose	39.0 (14.3)	38.2 (17.5)	-0.8 (13.6)	[-4.8; 3.1]	NA
2 mg dose	42.0 (17.5)	36.4 (16.0)	-5.2 (15.3)	[-9.9; -0.6]	p = 0.679
Behavior Following Wakefulness					
Placebo	38.3 (18.2)	34.5 (15.3)	-5.0 (14.1)	[-9.3; -0.7]	
0.2 mg dose	41.6 (16.9)	37.4 (13.8)	-4.2 (17.1)	[-9.8; 1.3]	NA
0.5 mg dose	39.0 (12.8)	37.6 (14.9)	-1.2 (10.5)	[-4.3; 1.9]	NA
2 mg dose	40.9 (17.0)	37.3 (16.6)	-3.7 (14.5)	[-8.0; 0.6]	p = 0.658

4. The PP and ITT analysis show that in the dose ranging period all efficacy parameters **for responders** remain high and there is no difference between Circadin and placebo. In the ITT analysis of the non-responders a significant difference between Circadin 5 mg and placebo in variables – quality of sleep, awakening from sleep and % of nights scored "very good" or "good" was found.

Neurim V – A double blind, parallel group, randomised, placebo controlled, dose ranging study of efficacy and safety of Circadin in the improvement of sleep in adult insomniacs with a 6 month extension of open label Circadin 2mg administration for long-term assessment of safety and efficacy. This trial had the following structure:

Baseline period: single-blind, one-week, placebo run-in period;

Treatment period: double-blind, six-week, treatment period: patients randomly received Circadin 1 mg, 2 mg , 5 mg or placebo:

Extension period: open-label 26-week treatment period further extended to 12 months by a protocol amendment – patients received Circadin 2 mg per day;

Withdrawal period: 2 weeks follow-up where patients received no study medication;

Study duration: 7 weeks without the extension and up to 61 weeks including the extension and the withdrawal period.

The primary efficacy variable was quality of sleep (QOS) derived from the question 4 and 5 of the Leeds questionnaire. The secondary variables were the remaining parameters of the Leeds questionnaire and sleep diary.

In this study the population entered were males or females with age ≥20 and≤80 years old suffering from primary insomnia according with the criteria of DSM-IV. 263 were randomised: 62 to 1 mg; 65 to 2 mg; 67 to 5 mg and 69 to placebo.

Results

The primary variable showed no significant difference in the ITT and PP population for the Circadin at 5 mg at 4 and 7 weeks.

The remaining analysis was done post-unblinding**.** Sub group analysis suggested efficacy in patients >55 years old.

- Main studies

The clinical development included 3 main efficacy studies, NEURIM VII, NEURIM IX and NEURIM VIIIa.
As already mentioned, study NEURIM VIII, a Circadin vs. placebo randomized, double blind study was planned before Neurim IX but never concluded given the poor rate of recruitment in all centers. (See discussion)

The three studies had the same design i.e. randomized, double blind, placebo control, parallel group, multicenter.
The enrolled patients were older than 55 years with a diagnosis of primary insomnia (DSM-IV). Patients were receiving evaluation to rule out the presence of depression (Raskin), anxiety (Covi) and Dementia (Mini Mental State).
Patients suffering from severe neurological, psychiatric or neurosurgical diseases were excluded. Also patients on CNS medications or benzodiazepine users were excluded.

Enrolled patients were treated for 2 weeks with placebo (single blind, run-in phase).

At the end of this period responders to placebo (LSEQ-QOS ≤ 40mm), were excluded from any efficacy analysis. In addition patients with positive urine drug test (BZD, non-BZD hypnotics), with poor compliance (<70% or >130%) or incorrect use of the assessment tools (diary & LSEQ) were also excluded.

The remaining subjects were undergoing randomization and double blind treatment with either Circadin or placebo for 3 weeks.
At that time final evaluation of efficacy and safety was performed.

Statistical Methods: In all clinical studies, data handling and analysis followed standard accepted practice; parametric (ANOVA, Man-Whitney test, t-test) and non-parametric (chi square, Fisher's exact, Kruskal-Willis test etc.) tests were used as appropriate.

METHODS

NEURIM VII. Phase III Study: A double -blind, Parallel Group, Randomised, Placebo Controlled Study of Efficacy and Safety of Circadin 2 mg in the Improvement of Sleep in >55 year Old Insomniacs.

Study Participants
To be eligible for the study, patients were required to satisfy the following criteria at visit 1:

- Male or female aged ≥55 years
- Suffering from primary insomnia (DSM-IV criteria), and for whom this is the consultation complaint.
- Confirmed diagnosis of primary insomnia (Sleep History Questionnaire given to the patient before visit 1)

In addition, patients had to satisfy the following criteria at visit 2:

- Establish baseline pathology (Leeds SEQ)
- Good compliance during the 2-week placebo run-in period defined as 70% to 130% of prescribed tablets
- Correct use of Sleep Diary & Leeds SEQ
- Negative drug screen (BZD & non-BZD Hypnotics)

Treatments
Circadin tablets 2 mg once daily, after food and preferably 1-2 hours before going to bed (21.00 - 22.00)
The study comprised 3 periods: *period 1* was a two week run in with placebo, *period 2* was a randomised, double blind, placebo controlled, parallel group treatment period of 3 weeks and *period 3* was a two week withdrawal period with placebo.

Objectives
The objective was to evaluate the efficacy and safety of Circadin 2mg tablets on the quality of sleep (QOS) and behaviour during the day, in adult insomniac out -patients, aged 55 years or more, including the elderly.

Outcomes/endpoints
The primary efficacy endpoint in this study was QOS, derived as the mean of Questions 4 and 5 of the LSEQ.

The secondary endpoints were the remaining derived parameters from the LSEQ and the sleep diary parameters (QON and QOD).

Randomisation
All patients received placebo for a single-blind, two-week, run-in period. Patients who fulfilled the inclusion and exclusion criteria were then randomised in a 1:1 ratio to receive either Circadin® 2 mg or placebo for a period of three weeks. Following the double-blind active treatment period, patients received placebo during a two-week, single-blind, run-out period. One tablet of medication was self-administered on a daily basis, one to two hours before going to bed.

NEURIM IX. A double-blind, parallel group, randomised, placebo controlled study of efficacy and safety of Circadin 2 mg in the improvement of sleep quality in insomnia patients aged 55-80 years.

Study Participants

Inclusion criteria: same as study NEURIM VII.
Exclusion criteria:
-Severe neurological, psychiatric disorder (especially psychosis, depression or anxiety) & alcohol
-Excessive consumption of coffee or tea
-Positive HIV or chronic active viral hepatitis
-History or current drug & alcohol abuse
-History of severe cardiac disorder

Treatments
Circadin tablets 2 mg once daily, after food and preferably 1-2 hours before going to bed (21.00 - 22.00)

The study comprised 2 periods: *period 1* was a two week run in with placebo, *period 2* was a randomised, double blind, placebo controlled, parallel group treatment periods of 3 weeks

Objectives
Evaluate efficacy and safety of Circadin 2 mg in the improvement of sleep quality in insomnia patients aged 55-80 years.

Outcomes/endpoints
Primary efficacy endpoint: To compare, at the end of the 3-week treatment period, the rate of responders in the Circadin vs placebo groups. The responders are 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 is considered to be of clinical importance and relevance.

Secondary efficacy endpoints: Quality of sleep (LSEQ-QOS and Pittsburg sleep quality index (PSQI)-COMP1), Sleep latency (LSEQ-GTS and PSQI-Q2), Daytime functioning (LSEQ-BFW and score from WHO-5 well being index) and score on clinical global impression scale (CGIS).
Sample size
800 patients were planned to be screened to enable an estimated 520 randomised patients and 332 patients (166 patients in each treatment arm) to be included in the Full Analysis Set to receive active drug or placebo for three weeks.

Randomisation
Eligible subjects underwent a two-week single-blind placebo run-in period prior to Visit 2. Participants who fulfilled eligibility criteria were then randomised in a 1:1 ratio to receive either Circadin 2 mg or placebo in a double-blind manner. Following a three-week intervention period, subjects underwent a final assessment at Visit 3.

NEURIM VIIIa. A double-blind, parallel group, placebo controlled, randomised study comparing the effects of zolpidem 10 mg and placebo in the improvement of sleep quality in insomnia patients aged 55 years and over

Study Participants
To be eligible for the study, patients were required to satisfy the following criteria at visit 1:

- Patients aged ≥ 55
- Suffering from primary insomnia (DSMIV – 307.42), characterized by poor quality of sleep

In addition, patients had to satisfy the following criteria at visit 2:

- Lack of significant placebo response during the run-in period (≥ 40mm in LSEQ-QOS mean value)
- Negative drug screen (BZD & non-BZD Hypnotics)

Exclusion criteria: same as NEURIM IX

Treatments
Zolpidem 10 mg tablet taken orally once daily before going to bed.
The study comprised 2 periods: *period 1* was a two week run in with placebo, *period 2* was a randomised, double blind, placebo controlled, parallel group treatment periods of 3 weeks.

Objectives
To demonstrate the sensitivity & validity of the assessment tools in the Circadin pivotal studies ie LSEQ & diary, by using them to measure sleep & daytime consequences of a well known insomnia drug (zolpidem 10 mgr)

Outcomes/endpoints

Primary efficacy objective: to evaluate, compared to placebo, the effects of Zolpidem 10 mg on Quality of night (QON) derived from the diary.

Secondary efficacy objectives:
% responders (LSEQ – QOS & BFW), change from baseline of LSEQ – QOS, BFW, GTS, AES, QOD (diary), PSQI & and quality of life score from SF-12v2™

Sample size
It was planned to enrol 200 patients into the run-in in order to obtain 110 patients, 55 patients per treatment arm, treated with active drug or placebo for 3 weeks.

Randomisation
After screening, all enrolled patients entered a single-blind, two-week run-in period during which they took one placebo tablet each evening. All patients who then fulfilled the pre-treatment eligibility criteria were randomised to either Zolpidem 10 mg or placebo in a 1:1 ratio and entered the double-blind treatment period.

RESULTS

Participant flow / Numbers analysed
Neurim VII:
188 were randomised, 94 for each treatment group. Following an initial analysis of this total patient population, it was found that sixteen patients failed to satisfy major entry criteria and were randomised by error and therefore excluded. Two patients were excluded from the ITT population, one because he took no medication and the other due to lack of double-blind efficacy data. The ITT population was thus comprised of 170 patients. Of these, 82 patients were randomised to Circadin 2 mg and 88 to placebo. Of these, 78 of the patients randomised to Circadin and 86 of the patients randomised to placebo, completed the study.

Neurim IX:
1208 subjects completed sleep questionnaire, 523 patients entered the study, 453 were randomised and 334 patients were included in the Full Analysis Set, 169 in the Circadin group and 165 in the placebo group. Of the 453 randomised patients, 99 were placebo responders during run-in and were included in the Placebo Responder population, 48 in the Circadin group and 51 in the placebo group. In the Combined Full Analysis & Placebo Responder Set Low 6-SMT Sub-population (< 8) there were 196 patients; of these 145 were in the Full Analysis Set Low 6-SMT Set sub-population.

Text Table 3: Summary of Populations

	Circadin		Placebo		Total	
	N	%	N	%	N	%
Safety	225	(100%)	228	(100%)	453	(100%)
Full Analysis Set	169	(75%)	165	(72%)	334	(74%)
Low 6-SMT (<=8)	73	(32%)	72	(32%)	145	(32%)
High 6-SMT (> 8)	96	(43%)	93	(41%)	189	(42%)
Per Protocol	166	(74%)	161	(71%)	327	(72%)
Per Protocol Low 6-SMT (<=8)						

	Circadin		Placebo		Total	
	N	%	N	%	N	%
	71	(32%)	69	(30%)	140	(31%)
Combined Full Analysis & Placebo Responder						
	217	(96%)	216	(95%)	433	(96%)
Combined Full Analysis & Placebo Responder - Low 6-SMT (<=8)						
	95	(42%)	101	(44%)	196	(43%)
Placebo Responder						
	48	(21%)	51	(22%)	99	(22%)

Neurim VIIIa
289 patients were screened and 179 entered the single-blind run-in period and were treated with run-in medication. Of these 144 were in the safety analysis set and 114 patients completed the double-blind treatment period and are included in the Full Analysis Set.

Overall, in the two Circadin studies (Neurim-VIII & Neurim- IX) 1186 patients were enrolled in the run-in phase. From those 965 were randomized and 767 completed the studies. From those, only 334 (Neurim-IX) were included in the efficacy analysis set, of whom 169 had been treated with Circadin and 165 with placebo. In the active comparator study (zolpidem 10 mg) the respective numbers are 179 enrolled and 114 completed (57 on zolpidem and 57 on placebo).

Comparable for the three studies is the attrition rate in the enrollment process from enrolled to randomized to completed patients as well as the ratio of patients per center and these numbers are very close to the Neurim-VII numbers, as can be seen in the following table (Table 1).

Study	Enrolled	% Randomized	% Completed	Completed / # centers
NEURIM-VII	222	84%	73%	3.5
NEURIM-VIIIa	179	83%	64%	2.65
NEURIM-VIII	663	77%	65%	3.5
NEURIM-IX	523	87%	64%	UK only

Recruitment
The list of patients excluded from enrolment because of failure in the screening procedure and the reasons for that failure is shown in the tables below.

Neurim VII

Reason	***Number of subjects***
Secondary insomnia due to mental disorder (Anxiety/Depression)	9
Secondary insomnia due to general medical condition (illness)	1
Absence of primary insomnia characterized by poor sleep quality	48
Circadian Rhythm Sleep Disorder Jet Lag Type	1
Age < 55	1
Total	**60**

Neurim IX

Reason	***Number of subjects***
Secondary insomnia due to mental disorder (Anxiety/Depression)	37
In other study	6
Forbidden medications	121
Patient not wishing to take part	171

Absence of primary insomnia characterized by poor sleep quality	1
Secondary insomnia due to general medical condition (pain, restless leg syndrome)	3
Work variable hours	1
Drink alcohol above the limit	2
Positive questionnaire but patients did not enter the study	192
Serious health problems	72
Telephone screen not completed but no obvious reason why responses have stopped. Patient did not Enter.	60
Those which have IDs but are completely blank	14
Weight – out of allowed BMI range	12
Total	**692**

Outcomes and estimation

- Neurim VII:

Primary parameter

In this study 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 between the two arms in the same variable was 5.97 mm (P=0.047). The difference for LSEQ-BFW score at the end of the treatment was 8.87 mm favoring Circadin (P=0.002). These results are summarised in the following 2 tables:

Table 12: Quality of sleep (QOS) – in the Leeds SEQ - ITT population – Neurim VII

	Placebo	**Circadin 2 mg**
Number of patients	88	82
Baseline Mean (sd) in mm	65.1 (11.9)	65.3 (12.1)
Week 4 change: Mean (sd)	-16.5 (17.8)	-22.5 (20.7)
Treatment difference (sed)		-6.0 (3.0)
95% Confidence Interval		(-11.9, -0.1)
p-value treatment		**0.047**

Table 13: Behaviour following waking (BFW) - in the Leeds SEQ ITT population - Neurim VII

	Placebo	**Circadin 2 mg**
Number of patients	88	82
Baseline Mean (sd) mm	56.9 (15.4)	59.9 (13.8)
Week 4 change: Mean (sd)	-6.8 (16.1)	-15.7 (20.2)
Treatment difference (sed)		-8.9 (2.8)
95% Confidence Interval		(-14.5, -3.3)
p value treatment		**0.002**

Secondary parameters

Significant difference has been reported for the diary variable QON, the mean change of 0.42 favoring the active treatment arm (P=0.003).

No significant results have been reported for LSEQ-GTS & AFS as well as Diary-QOD and the SF-36.

- Neurim IX

Primary endpoint

The results show higher response rate (improvement in LSEQ-QOS & BFW≥10mm) in the arm of Circadin (26% vs. 15%, p=0.014). See table below:

Table: Improvement of ≥ 10 mm on the QOS and BFW scales of the LSEQ – full analyses population

	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				

The impact of baseline severity on responder rate is shown in the following table:

Table: Impact of baseline severity on Responder Rate to Circadin vs. Placebo

Neurim IX study	**% Responders**			
Severity Index (N)	**Circadin**	**Placebo**	**Difference**	**Odds ratio**
Total population	26%	15%	11%	1.97
PSQI> 5 (N= 334)				
Severe Insomnia	27.4%	15.5%	11.8%	2.05
PSQI> 11 (N=161)				
Very Severe insomnia PSQI> 13 (N=48)	28.5%	10%	18.5%	3.59

These results show that the difference in response rate between Circadin and placebo is increased by 11.8% in patients with severe insomnia (odds ratio of 2.05) and by 18.5% in the very severe insomnia population (odds ratio of 3.6), suggesting that the therapeutic benefit of Circadin is higher in the very severely ill.

Secondary endpoints

There is an average of 4mm difference between Circadin and placebo improvement (baseline vs. EOT) in LSEQ-QOS. (p=0.014). Another statistically significant result is the effect on functioning when awake (LSEQ-BFW), but again the mean difference of improvements with CIRCADIN or placebo was 3mm (p=0.038).

Other statistically significant results are the LSEQ-GTS (difference of 3.3mm, p=0.013), the PSQI-Component1 evaluating quality of sleep (difference 0.2, p=0.036), PSQI- Component2 evaluating sleep latency (difference 8.8 min, p=0.028) and WHO-5 well being questionnaire (difference 0.8, p=0.034). The results are summarised below:

Table of statistically significant secondary endpoints – full analysis population

Domain	Endpoint	Mean Difference (95% CI)	p-value
Sleep Quality	Leeds QOS	-4.0 (-7.2, -0.8)	0.014
	PSQ1 Component 1	-0.2 (-0.3, -0.0)	0.036
Sleep Latency	Leeds GTS	-3.3 (-5.8, -0.7)	0.013
	PSQ1 Question 2	-8.8 (-16.07, -1.0)	0.028
Daytime Functioning	Leeds BFW	-3.0 (-5.9, -0.2)	0.038
	WHO 5 Well-Being Index	0.8 (0.1, 1.5)	0.034
Other	Sleep Diary night sleeping score	0.2 (-0.0, 0.3)	0.054
	PSQ1 global score	-0.6 (-1.3, 0.1)	0.081

- Neurim VIIIa

Primary efficacy parameter

The main results are summarised below.

Sleep Diary

Table: Quality of Night: End of Treatment and Change from Baseline

	Full Analysis Set			Per Protocol Population		
	Zolpidem (n=57)	**Placebo (n=57)**	**Total (n=114)**	**Zolpidem (n=55)**	**Placebo (n=50)**	**Total (n=105)**
Baseline [a]						
n	57	57	114	55	50	105
Mean (± SD)	2.6±0.7	2.4±0.7	2.5±0.7	2.6±0.7	2.4±0.7	2.5±0.7
Range	1-4.3	1-4	1-4.3	1-3	1-3	1-3
EOT [b]						
n	57	57	114	55	50	105
Mean (± SD)	3.6±0.8	2.8±0.9	3.2±0.9	3.6±0.8	2.9±0.9	3.2±0.9
Range	1.7-5	1-5	1-5	1.7-5	1-5	1-5
Change from baseline						
n	57	57	114	55	50	105
Mean (± SD)	1±0.8	0.5±1	0.7±0.9	0.9±0.8	0.5±1	0.7±0.9
Range	-1-2.7	-1.7-3	-1.7-3	-1-2.7	-1.7-3	-1.7-3
Treatment diff.	0.5			0.43		
95% CI	0.17-0.83			0.08-0.78		
p-value (t-test)	0.003			0.016		

Data Source: Tables C.4.1.1, C.4.1.2, D.4.1.1, D.4.1.2
[a] baseline was the end of the run-in period (Week 2)
[b] End of Treatment was the end of the period (Week 5)

Secondary objectives

LSEQ:

Table: Quality of Sleep: End of Treatment and Change from Baseline (FA, PP)

	Full Analysis Set			**Per Protocol Population**		
	Zolpidem (n=57)	**Placebo (n=57)**	**Total (n=114)**	**Zolpidem (n=55)**	**Placebo (n=50)**	**Total (n=105)**
Baseline [a]						
n	57	57	114	55	50	105
Mean (± SD)	62.6± 12.6	62.1±13.8	62.4±13.1	62.3±12.7	62.9±13.9	62.6±13.2
Range	40.7-97.2	40.5-95.7	40.5-97.2	40.7-97.2	40.5-95.7	40.5-97.2
EOT [b]						
n	56	54	110	54	48	102
Mean (± SD)	36.7±17.6	49.6±19.3	43.1±19.5	36.5±17.5	49.8±20.4	42.7±20
Range	6.5-86.8	5.2-95.2	5.2-95.2	6.5-86.8	5.2-95.2	5.2-95.2
Change from baseline						
n	56	54	110	54	48	102
Mean (± SD)	-25.9±21.5	-12.9±20.9	-19.5±22.1	-25.9±21.7	-13.3±22	-20±22.6
Range	-76.8-39.7	-84.3-26.5	-84.3-39.7	-76.8-39.7	-84.3-26.5	-84.3-39.7
Treatment diff.	-13.01			-12.63		
95% CI	-21.03- -4.99			-21.23- -4.038		
p-value (t-test)	**0.0017**			**0.0044**		

Data Source: Tables C.4.2.2.1, C.4.2.2.2, D.4.2.2.1, D.4.2.2.2

[a] baseline was the end of the run-in period (Week 2)

[b] End of Treatment was the end of the period (Week 5)

In both the FAS and PP populations, there was a statistically significant difference in Quality of Sleep between the treatment groups in favour of Zolpidem (p=0.002; p=0.004).

Table: Getting to Sleep: End of Treatment and Change from Baseline (FA, PP)

	Full Analysis Set			Per Protocol Population		
	Zolpidem (n=57)	Placebo (n=57)	Total (n=114)	**Zolpidem** (n=55)	Placebo (n=50)	Total (n=105)
Baseline [a]						
n	57	57	114	55	50	105
Mean (± SD)	60.7±13	62.1±13.4	61.4±13.1	60.4±13.1	62.2±14	61.2±13.5
Range	20.8-88.8	22-96.3	20.8-96.3	20.8-88.8	22-96.3	20.8-96.3
EOT [b]						
n	56	54	110	54	48	102
Mean (± SD)	39.5±20.7	50.3±16.4	44.8±19.4	39.3±21	50.1±17.2	44.4±19.9
Range	6.7-96.4	13-90.4	6.7-96.4	6.7-96.4	13-90.4	6.7-96.4
Change from baseline						
n	56	54	110	54	48	102
Mean (± SD)	-21.1±20.4	-11.9±17.9	-16.6±19.7	-21±20.6	-12.4±18.8	-17±20.1
Range	-61.7-22.6	-58.9-21.8	-61.7-22.6	-61.7-22.6	-58.9-21.8	-61.7-22.6
Treatment diff.	-9.14			-8.58		
95% CI	-16.41- -1.88			-16.37- -0.8		
p-value (t-test)	0.014			0.031		

Data Source: Tables C.4.2.4.1, C.4.2.4.2, D.4.2.4.1, D.4.2.4.2

[a] baseline was the end of the run-in period (Week 2)

[b] End of Treatment was the end of the period (Week 5)

Table: Responder Rates (QOS+BFW*) (FA, PP)

	Full Analysis Set			Per Protocol Population		
	Zolpidem (n=57)	**Placebo (n=57)**	**Total (n=114)**	**Zolpidem (n=55)**	**Placebo (n=50)**	**Total (n=105)**
Number of responders	31	14	45	30	13	43
% of responders	55.4%	25.9%	40.9%	55.6%	27.1%	42.2%
χ^2 (1) p-value	9.85 **0.002**			8.45 **0.005**		

Data Source:Tables C.4.2.1.1, C.4.2.1.2, D.4.2.1.1, D.4.2.1.2

* Responders are patients who had 10 mm improvement from baseline in the VAS score in QOS derived as the mean of questions 4 and 5 and BFW derived as the mean of questions 8, 9 and 10 of the Leeds SEQ

In summary, Zolpidem (10 mg dose) has demonstrated

- A significant effect on the primary efficacy parameter Quality Of Night in patients with primary insomnia aged >55 years (P=0.003). Zolpidem has been reported to improve the quality of sleep in a 7-21 days treatment periods with minimal adverse effects on daytime functioning. Our results obtained with the diary as the main tool confirm the known positive effect of Zolpidem on sleep quality.
- A significant effect of Zolpidem as assessed by the LSEQ QOS variable is demonstrated (p=0.002), in agreement with the medical knowledge on improvement in sleep quality with this drug.
- A significant improvement of the LSEQ variable Getting to sleep (GTS) as compared to placebo (p=0.014) is also demonstrated, in agreement with the medical knowledge on improvement in sleep latency with this drug.
- A significantly higher responder rate compared to placebo (p=0.002) is also demonstrated with Zolpidem.
- A significant correlation (p<0.0001) between the QOS parameter of the LSEQ and component 1 of the PSQI and between the BFW parameter of the LSEQ and component 7 of the PSQI was found.

However, Zolpidem did not demonstrate a significant effect over placebo in the daytime variables BFW, AFS of the LSEQ and QOD of the Diary, which is also in agreement with the medical knowledge on the lack of daytime effects with this drug.

Regarding safety, of the 144 patients in the safety population, 24 patients (17%) reported AEs during the double-blind phase, 14 (18.4%) patients in the Zolpidem group and 10 (14.7%) in the placebo group. The most commonly reported AEs were diarrhoea, vomiting and hyperlipidemia each experienced by two patients in the Zolpidem group.

The safety results demonstrate that Zolpidem 10 mg is quite safe and are consistent to general medical knowledge.

- Analysis performed across trials (pooled analyses and meta-analysis)

Baseline data

In order to determine if the run-in period that selected out 16% of the potential patients might have produced a selection bias in the population studied, the applicant performed a pooled analysis in which entry criteria failures ("placebo responders) were included. The data are shown in the table below demonstrate that the selection method did not compromise the applicability of the results in the Circadin clinical trials.

Table: Pooled analysis of responder rate in Neurim pivotal studies including the 93 patients who are entry criteria failures and had data available

Pooled analysis Neurim I, VII, IX with data on patients who failed to confirm entry criteria	**Placebo (N=322)**	**Circadin 2 mg (N=308)**
% Responders	18%	29%
Difference between the two arms	11%	
Odds Ratio for Circadin over placebo	1.86	
95% Confidence Interval	4.3%, 17.5%	
p value treatment	p=0.001	

Primary endpoint
The size of the primary endpoint expressed as the rate of responders, which includes two criteria – the quality of sleep and the impact on morning alertness in show below in a pooled analysis

Table: Primary Efficacy Endpoint: Responder Rate Analysis of Circadin vs. Placebo in Quality of Sleep (QOS) and Behavior Following Wakefulness (BFW).

Study	**Neurim VII**		**Neurim IX**		**Pooled analysis (Neurim I, VII, IX)**	
Treatment	**placebo**	**Circadin**	**placebo**	**Circadin**	**placebo**	**Circadin**
N	88	77	164	168	**272**	**265**
Number (%) Responders	24 (27%)	36 (47%)	25 (15%)	44 (26%)	**51 (18.7%)**	**86 (32.4%)**
Difference from Placebo	20%		11%		**14%**	
P value	0.0095		0.014		**0.0003**	

Secondary endpoints

A pooled analysis on the quality of sleep and morning alertness is shown below.

Table: % responders to Circadin vs Placebo showing concomitant and clinically meaningful improvement in quality of sleep and morning alertness, and in each of them separately. Pooled Analysis (Neurim I, VII, IX)

	QOS&BFW responders		**QOS responders**		**BFW responders**	
Treatment	**Circadin**	**placebo**	**Circadin**	**placebo**	**Circadin**	**placebo**
N	265	272	265	272	265	272
Responders %	**32.4%**	18.7%	**48%**	34.5%	**40.3%**	30%
Difference	14%		13.5%		10.3%	
Odds ratio	2.08		1.75		1.57	
P value	0.0003		0.0017		0.012	

The comparison of the mean change in subjective sleep latency (in min) between Circadin, zolpidem and placebo is summarised in the following table:

Table: Mean change in Subjective Sleep Latency (in min) with Circadin zolpidem and placebo in Circadin target patient population

	Circadin 2 mg (Neurim IX)	**Circadin 2 mg (Neurim IX)**	**Zolpidem 10 mg (Neurim VIIIa)**
Age and subgroup	**> 55**	**> 55 Low 6-SMT**	**> 55**
N (active treatment)	169	73	63
N (placebo treatment)	165	72	58
Mean Baseline Sleep Latency, minutes	65.1	56.5	58.3
Mean change Placebo	-12.9	-9.7	-8.6
Mean change comparator	-24.3	-26.4	-25.9
Difference from placebo, minutes	**- 8.8***	**-18.5***	**-17.3**
P	0.028	< 0.001	0.028

*Analysis of covariance adjusted to baseline

As seen in the above table, the subjective shortening of sleep latency with Circadin 2 mg vs. placebo in the total population is somewhat lower than that of zolpidem 10 mg and is similar to that of zolpidem 10 mg in the subpopulation of patients with low endogenous melatonin (low 6-SMT; excreting <8 microgram 6-SMT excreted per night).

Circadin and zolpidem treatment had positive effects on quality of sleep (QOS) and quality of night (QON), as shown in the table below.

Table: Effects of Circadin 2 mg and Zolpidem 10 mg vs. Placebo on Quality of Sleep (LSEQ QOS) and Sleep Quality Ratings (QON; 5 categorical units)

Parameter	***Neurim VII change from BL***	***Neurim VIIIa change from BL***
QOS (mm)	Circadin **-22.5**±20.7 Placebo -16.5±17.8 ; P=0.047	Zolpidem **-25.9**±21.5 Placebo -12.9±20.9; P=0.0017
QON (5 units)	Circadin **0.9**±0.8 Placebo 0.46±0.97; P=0.003	Zolpidem **1.0**±0.8 Placebo 0.5±1; P=0.003

Subpopulation analyses
The sleep latency and quality in the Full Analysis Set (N=334) and in the low 6-SMT sub-population of the Full Analysis Set (N=145) is compared in the table below:

Table: Sleep latency and quality with Circadin vs. placebo in the Full Analysis Set (N=334) and low 6-SMT sub-population of the Full Analysis Set (N=145)

Endpoint ***Full Analysis set***	***Placebo*** ***N=165***	***Circadin*** ***N=169***	***Mean Difference**** ***(95% CI)***	***p-value***
Sleep Latency Minutes	-12.9 (39.7)	-24.3 (47.6)	-8.8 (-16.7, -1.0)	0.028
Sleep Quality Score (PSQI component 1)	-0.4 (0.8)	-0.6 (0.9)	-0.2 (-0.3, -0.0)	0.036

Sleep Quality (LSEQ QOS)	-4.2 (14.7)	-8.6 (16.3)	-4.0 (-7.2, -0.8)	0.014
Endpoint ***Low 6-SMT set***	***Placebo*** ***N=72***	***Circadin*** ***N=73***	***Mean Difference*** ***(95% CI)***	***p-value***
Sleep Latency Minutes	-9.7 (33.2)	-26.4 (43.9)	-18.5 (-29.0, -7.9)	<0.001
Sleep Latency Score (PSQI component 2)	-0.2 (0.9)	-0.6 (1.0)	-0.3 (-0.6, -0.0)	0.027
Sleep Quality (LSEQ QOS)	-3.7 (16.1)	-9.4 (17.5)	-5.9 (-11.1, -0.7)	0.025

*Analysis of covariance adjusted to baseline

The similarity in efficacy of Circadin on the quality of sleep in the full analysis population and its subpopulation of patients with low 6-SMT confirms that age is a good surrogate marker of melatonin deficiency in the primary insomnia patient population. Thus, further measurements of endogenous 6-SMT levels in the primary insomnia population; over 55 years of age, would not be necessary in clinical practice.

- Clinical studies in special populations

Elderly
Despite the inexistence of a specific trial in the elderly, the efficacy has been documented in a pooled analysis from the ITT population. The data are presented below:

Table: % response to Circadin vs. placebo by age (pooled analysis ITT)

	Age > 55 (mean age 66)		Age 55-65 (mean age 60)		Age > 65 (mean age 72)	
Treatment	Circadin	placebo	Circadin	placebo	Circadin	placebo
N	**265**	**272**	**120**	**136**	**145**	**136**
Responders %	**32.4%**	**18.7%**	**33.3%**	**18.3%**	**31.7%**	**19.1%**
Difference	**14%**		**15%**		**12.6%**	
Odds ratio	**2.08**		**2.2**		**1.96**	
P value	**0.0003**		**0.006**		**0.015**	

The effect size did not seem to change across age ranges. Furthermore the overall population is already selected for those above 55 years of age.

Patients under hypnotic medicines (benzodiazepines)
A subgroup analysis taking in account the status as BZD users and non-users was performed. Data was collected in the 2 pivotal out-patient studies Neurim VII and IX and an analysis was performed for the primary parameter, rate of responders that includes two dimensions – the quality of sleep and the impact on morning alertness. These data are summarised in the table below:

Table : Primary Efficacy Endpoint: Responder Rate Analysis of Circadin vs. Placebo in Quality of Sleep (QOS) and Behavior Following Wakefulness (BFW) in prior hypnotic users and non uswers (ITT population Neurim VII and IX).

Study	**Prior hypnotic use**		**No prior hypnotic use**	
Treatment	**Circadin**	**placebo**	**Circadin**	**placebo**
Responders	23	11	57	38
Non responders	31	53	134	150
Chi square		9.22		4.68
P value		**0.002**		**0.03**

- Supportive studies

- **End stage renal disease on chronic hemodialysis:**

Design – Open label, 3 weeks duration. Participants 8 patients (7M, 1F, 23-61 year old)
Results – No accumulation of melatonin in the blood has been observed, between week 1 & 3. Patients improved arithmetically according to PSQI Global.

Main effect is improvement in Component-7 (daytime functioning). Concerning safety, no serious AEs reported, one patient experienced insomnia and dropped out (due to study medication according to the PI). No significant laboratory tests findings.

- **Patients with Nocturnal Hypertension:**

Design – Randomized, double blind, placebo controlled, 8 weeks duration (2 run-in single blind placebo, 4 treatment & 2 run-out open). 38 patients randomized (42% female & age 42-83).
Results – 58% patients on CIRCADIN responded (≥5mm Hg decrease in mean night systolic BP) vs. 21% on placebo. Reduction in nocturnal BP CIRCADIN > placebo (p=0.01). Improvement but not statistically significant in quality of sleep and morning alertness was observed in the CIRCADIN arm.

- **Patients suffering from type II diabetes & complaining of insomnia:**

Design – Randomized, double blind, placebo control, 6 months treatment period. 42 patients randomized (55% female & age 50-76).
Results – Sleep Efficiency & Wake After Sleep onset improved vs. baseline ($p<0.02$). Decrease in HbA1C level vs. baseline, but not statistically significant. When data were combined with study 951005 (same protocol) then this parameter reached statistical significance.

- **Elderly patients suffering from insomnia and treated with benzodiazepines.**

A randomised double-blind crossover study comparing the efficacy of melatonin controlled release (2 mg once daily) versus placebo in a 3 week treatment 21 pt were enrolled: age from 55 to 95 years old; diagnosis insomnia and at least intake of a tablet of Benzodiazepines/day. Efficacy evaluated by sleep quality monitored through wrist actigraphy. Melatonin produced the following effects: 13.6% improvement in sleep efficiency; 59.8% reduction in sleep latency, 48.5% reduction in wake time after sleep onset, 9.4% increase in total sleep time, 29.4% reduction in number of awakenings.

- **Insomnia patients discontinuing chronic used of benzodiazepines.**

A randomised double-blind parallel group study of controlled-release melatonin (2 mg) versus placebo. 6-week treatment. 34 pt were enrolled; age from 40 to 90 years old; diagnosis insomnia, at least intake of a tablet benzodiazepines/d and willingness to withdrawn benzodiazepines. Efficacy criteria: tapering and discontinuation of BZ assessed by patients diaries and sleep quality assessed by a daily questionnaire.

In the DB period 14/18 pt stopped taking BZ under Circadin against 4/16 in the placebo group. At six week the mean consume of BZ tablets was 0.15 for the Melatonin group and 0.48 for the placebo group.

Quality of sleep scores were higher in patients in melatonin than on placebo: 7.38 vs. 6.06. After the single blind period (all pt received melatonin) the rate of discontinuation of BZ was no different in the melatonin and the placebo group. At 6 months 19/24 pt that discontinued BZ maintained good sleep quality without BZ.

- **Patients with Benign Prostate Hyperplasia**

A unicenter, randomized double -blind, two parallel group study of Circadin™ (5 mg, once daily) versus placebo in a 6 months treatment and a 12 months extension of single blind treatment with prolonged-release melatonin. Fifty nine (59) Benign Prostate Hyperplasia patients (age 50--79) enrolled the study. All (59) patients were randomised, 57 concluded the double -blind treatment period and 50 concluded the 2 x 6 months of the long-term extension period of the study.
The results of daily treatment of 57 BPH patients for 6 months with prolonged-release melatonin (5 mg) indicated no significant improvement of the prostate disease over placebo.
The use of prolonged-release melatonin appears to be safe in terms of general safety, and endocrine homeostasis. Circadin appears to be safe in long term (50 patients 12 months beyond the 6 months of period I) treatment. Upon the long-term treatment, the prostate disease has not worsened and symptoms scores as well as quality of life improved.

Discussion on clinical efficacy

In the initial application (in 2000), the clinical efficacy and safety of Circadin was supported mainly by one pivotal clinical trial (Neurim VII). This was a phase III double-blind, randomized (3-week treatment), placebo controlled study of efficacy and safety of Circadin 2 mg in the improvement of sleep in ≥55 years old insomniacs.
Although a statistical significant result of Circadin 2 mg on the target population was obtained on the primary efficacy parameter (QOS subjectively assessed by the Leeds SEQ, p=0.047), this trial was seen as insufficient to stand alone in supporting the efficacy of Circadin given the background of equivocal results, the use of a primary analysis that uses just a subset of the items of the Leeds questionnaire and the difficulty in demonstrating that the statistical difference was indeed clinically relevant. In addition, the existence of a placebo run-in period might have induced some selection bias.
After the withdrawal, the Applicant requested formal Scientific Advice, which finally was completed in September 2002.

The main recommendations of the **Scientific Advice** were as follows:

1. *Indication* –" Primary insomnia characterized by poor quality of sleep is an appropriate target for drug development
2. *Primary Efficacy outcome measure* : Responder rate – a responder demonstrates an improvement by 10 mm or more on both the QOS and BFW scales of the LSEQ
3. *Measurement tools:* LSEQ as a primary tool, a confirmatory questionnaire-PSQI validated for 2 weeks, diary, and a quality of life questionnaire
4. *Secondary outcome measure:*
    a. A straightforward measure of the effect size in each treatment group and the absolute difference between groups in sleep quality, daytime functioning and quality of life.
    b. Use of an active comparator to help validate the outcome assessment tools in a pivotal clinical study. Comparator should be well studied, widely used in the European Community and have minimal adverse effects on daytime functioning.
5. Safety: *CPMP agreed that the anticipated extent of population exposure to Circadin would be sufficient to support the grant of a Marketing Authorization, provided that there are no unexpected safety data that would require further investigation.*

Dose-response studies
Neurim IV does not contribute to support the efficacy of Circadin in any dose in an unequivocal manner. The phase were a relevant effect size of therapeutic action is detected for Circadin 2 mg is non-controlled and the randomised phase of the trial is inconclusive.

The results of Neurim V are again inconclusive and the post-hoc analysis after unblinding cannot support a presumption of efficacy for which there is no strong evidence.

In the previous application, only NEURIM-IV was intended to be dose response. It showed that patients not responding to 2mg CIRCADIN became responders to 5mg, suggesting a dose response relationship. NEURIM-IV though was in general inconclusive and therefore the support it gives to the

dose response relationship is moderate. No additional dose response studies have been performed since this previous assessment.
Globally speaking the data collected in studies Neurim IV and V is hardly sufficient to clearly define the optimal dose. It is merely suggestive that a beneficial effect might occur for 2 mg in those older than 55 years.

These facts were debated extensively in the previous application as well as during the scientific advice. The conduct of future trials to confirm the putative effect with the dose of 2 mg was accepted at the applicant risk, despite the weak evidence to support the carry on of the dose of 2 mg over other possibilities, into pivotal trials and because of the reasonable safety profile.

Closure of Neurim VIII
The premature closure of Neurim VIII was of concern for the CHMP and was discussed at length. At diagnosis of primary insomnia (based on the SHQ) the average number of notifications issued by the company on each patient included in Neurim VIII was markedly and significantly higher than in Neurim VII (1.29+1.64 objections per patient in Neurim VIII compared to 0.64+0.98 in Neurim VII; p=0.000002). The large number of notifications per patient raised serious doubts about the diagnosis of primary insomnia in a significant proportion of the study population. At least 150 among the 433 (35%) completed patients in Neurim VIII have been identified as not suffering from primary insomnia. Overall, the decision to terminate the study was made on the accumulating evidence of poor eligibility of the patient population, unsatisfactory recruitment rate, organizational problems and concerns about the reliability of the data generated. The fact that the closure was not data driven has been demonstrated by the applicant. Furthermore the analysis made at request of CHMP if the study were to be counted showed that it would not impact negatively in the overall picture of the efficacy of Circadin.

Pivotal trials
Neurim VII was presented for evaluation still during the previous application. It is the first randomized controlled trial to achieve a statistical significant result of Circadin 2 mg on the target population. However this trial was seen as insufficient to stand alone in supporting the efficacy of Circadin given the background of equivocal results, the use of a primary analysis that uses just a subset of the items of the Leeds questionnaire and the difficulty in demonstrating that the statistical difference was indeed clinically relevant. In Neurim VII there is also one aspect of the design that might have induced some selection bias, which is the existence of placebo run-in period. Nevertheless Neurim VII is the first trial to produce a relative clean result that supports the efficacy of Circadin 2 mg in the population of those older than 55.

Neurim IX seen in perspective with Neurim VIIIa is a critical trial in this dossier because it should allow to prove or disprove the hints suggested by the exploratory studies and Neurim VII. It is awkward the applicant chose to adopt a trial design with a run-in placebo phase which is prone to induce selection bias. This is a crude technique based on the old concept of placebo effect, according to which placebo effect occurs early and disappears with time. In fact the recent studies suggest otherwise: despite the run-in period in Neurim VIIIa and Neurim IX there were 25.9% and 15% of placebo responders respectively. A run-in period to ascertain patients eligibility by disease criteria is not the same as explicitly excluding “placebo responders” based on a pre and post run-in comparison. While a run-in period is standard practice in many psychiatric fields, enrichment designs are not welcomed in pivotal trials. Fortunately the patients from Neurim IX were randomised thus making possible to reconstruct what would be a complete ITT population (Full analysis set + placebo responders). The data of this pooled analysis demonstrate that the selection method did not compromise the applicability of the results in the Circadin clinical trials.

The idea of conducting an independent trial to test zolpidem against placebo (Neurim VIIIa) instead of doing a 3 –arm trial is not the optimal solution. According to the scientific advice, the use of an active comparator would be intended to help validate the outcome assessment in a pivotal clinical study and in particular to demonstrate assay sensitivity. Nevertheless, even the test for assay sensitivity was compromised by the independent trial option. A 3-arm trial with an active comparator would have

given the opportunity of having an informative trial. However the logistics difficulties related with different administrations times and the need of double-dummy technique are acknowledged.
Taking into account these limitations, the characteristics of Neurim VIIIa and IX ended up being sufficiently similar to allow an indirect comparison, which although a suboptimal solution, provides some reassurance. Circadin performance seems to be indeed comparable to Zolpidem 10 mg and in some aspects can be better. Nevertheless the rate of responders in the zolpidem trial were much higher, in both groups, than in Neurim IX.

The main criticism, however, to the results of Neurim IX is that the effect size is relatively small. There are few responders overall and the difference from placebo is 11% (number needed to treat, NNT=9). In fact, the actual number of patients that benefit is small (a ¼ of those exposed), and they are already part of a selected population (those above 55 years of age).
However, the primary efficacy endpoint was endorsed by the CHMP through scientific advice. It is expressed as a rate of responders and includes two dimensions - the quality of sleep and the impact in diurnal behaviour.

Supportive studies suggest a therapeutic effect of Circadin in some patients with the obvious exception of the Prostate Hypertrophy study, which was not evaluating effects on sleep. However the population are not well characterized and the results are difficult to judge from the point of view of clinical significance. Furthermore the different studies present in the dossier suggest that melatonin produces an important-carry over effect. This makes crossover designs less suitable to assess the efficacy of melatonin formulations.

Overall the results in the different studies accumulated in this dossier suggest that the product is efficacious with a small effect size and in a relative small fraction of patients.

Clinical safety

- Patient exposure

The total patients exposure in Circadin (NEURIM studies) consists of 1361 patients in short term studies (1281 of them in the GCP studies I, IV, V, VII, VIII, IX and 30424) and the rest in the special population studies (951004, 951003 & 961009), 373 patients who received the compound for 6 months and 146 patients who received Circadin for one year or longer. If studies performed by independent investigators were included (N=46) then the total patients included in short term studies would increase to 1926.

- Adverse events

The table below describes the frequency of adverse events for the whole safety dataset (including the new studies VIII & IX). The most common adverse events were headache, pharyngitis, back pain, and asthenias, which were common, by MedDRA definition (>1/100, <1/10), both in the Circadin and placebo treated groups and were not necessarily related to treatment. No significant findings were described from the Physical Examination or from the Vital Signs recording.

Table: Most frequent adverse events in the whole safety dataset

	CIRCADIN			PLACEBO		
Body System / Adverse Experience	**N**	**%**	**Rate/100Pt weeks**	**N**	**%**	**Rate/100Pt weeks**
BODY AS A WHOLE						
Asthenia	42	3.3	0.28	24	2.0	0.51
Headache	68	5.3	0.45	76	6.4	1.62
Infection	21	1.6	0.14	8	0.7	0.17
Pain	21	1.6	0.14	13	1.1	0.28
Pain Abdominal	22	1.7	0.14	24	2.0	0.51
Pain Back	43	3.4	0.28	16	1.4	0.34
Pain Neck	14	1.1	0.09	7	0.6	0.15

DIGESTIVE						
Constipation	15	1.2	0.10	8	0.7	0.17
Diarrhea	16	1.3	0.10	15	1.3	0.32
Nausea	19	1.5	0.12	17	1.4	0.36
METABOLIC & NUTRITIONAL						
Weight Gain	12	0.9	0.08	15	1.3	0.32
MUSCULOSKELETAL						
Arthralgia	18	1.4	0.12	10	0.8	0.21
NERVOUS						
Anxiety	18	1.4	0.12	17	1.4	0.36
Dizziness	20	1.6	0.13	15	1.3	0.32
Dreams Abnormal	15	1.2	0.10	33	2.8	0.70
Insomnia	10	0.8	0.07	9	0.8	0.19
Migraine	15	1.2	0.10	15	1.3	0.32
RESPIRATORY						
Bronchitis	29	2.3	0.19	14	1.2	0.30
Pharyngitis	62	4.8	0.41	27	2.3	0.58
Rhinitis	30	2.3	0.20	26	2.2	0.55
SKIN						
Rash	12	0.9	0.08	4	0.3	0.09
GRAND TOTAL	**483**	**37.7**	**3.17**	**385**	**32.6**	**8.21**

- Serious adverse events/deaths/other significant events

19 Serious Adverse Events were registered including 3 deaths.

The 3 deaths were due to cardiopulmonary arrest, acute pulmonary oedema, and myocardial infarction and all three patients were receiving Circadin. None was considered related with the study compound.

The other 16 SAEs reported were of various causes: cerebrovascular disease, hyperthyroidism, hematuria and hydronephrosis, pelvic fracture, fractured wrist, ischaemic attack of the right lower limb, allergic reaction, syncope, elective surgery for worsening of venous insufficiency**,** acute antero-lateral myocardial infarction (subendocardic), duodenal sphincterectomy, fall following loss of consciousness, left tibia fracture, cholecystitis due to vesicular calculi, recurrent TIAs with right hemi-hypoesthesia and worsening of hypertension. Among them, 13 subjects were receiving Circadin at the moment of the onset of the SAE. All of them were considered not related to the compound.

- Laboratory findings

No significant melatonin-induced changes in laboratory parameters were found in short-term (3 weeks) or long-term studies (up to 18 month).

- Infections of the respiratory tract

An increase of the frequency of infections (of all kind) in Circadin treated subjects was recorded during the trial programme. This was attributed to the inclusion of long-term data from Neurim V protocol and was corrected by adjusting the rates of the adverse events for the extent of the exposure. After correction, the frequencies between the treated and the placebo groups appeared to be comparable. Nevertheless, the applicant committed to monitor this aspect in the periodic review of post-marketing events.

- Eye pathology

In one literature report, evidence of retinal toxicity after exposure to melatonin in a rat strain (albino rats) was described. However, no such finding was observed in the toxicology package performed by the applicant. In addition, the pooled clinical safety data containing nearly 2000 patients on Circadin does not contain any cases of retinal toxicity, nor any cases of visual acuity loss, dyschromatopsia, or altered light adaptation. While retinal toxicity represents an area of low potential risk based on

experience so far, post-marketing adverse event reports involving any form of visual disturbance will be closely monitored and examined specifically in PSURs.

- Loss of consciousness and related adverse events

Over 3 cases of fractures following falls in patients taking Circadin (reported as SAEs), 2 patients experienced a partial or complete loss of consciousness that was not temporally consistent with the fall. In one patient, the causality between study drug and loss of consciousness that caused the fall was not established.

Two of those patients were elderly with co-morbidities and taking other concomitant medications. In addition, one case of syncope not followed by fractures, but that caused hospitalisation, occurred in a patient while assuming Circadin. Also this patient was aged and took other medication for heart disease and other chronic conditions.Even though the events reported were considered not likely to have a causal relationship with Circadin, post-marketing surveillance will monitor adverse events, in particular loss of consciousness, and interactions with other drugs such as benzodiazepines.

- Safety in special populations

Elderly. Studies have been performed mostly in elderly, which constitute the target population
It is very likely that elderly patients present a number of co-morbidities and concomitant medications that have not been studied. A critical analysis of post marketing events is planned to allow ongoing evaluation.

Gender. Study 962001 results show that there is 3.3 to 4.2 fold increase in melatonin exposure in females as compared to males. However, no gender differences were found in the either cumulative maximal excretion of 6-SMT.

Children and Race. No studies have been provided

Patients with Cardiovascular Abnormality. An analysis of adverse events by cardiovascular disease status was performed. In this analysis were included patients from NEURIM-I, NEURIM-IV, NEURIM-V, NEURIM-VII, NEURIM-VIII & NEURIM-IX. A total of 599 patients on Circadin and 610 patients on placebo had at baseline a cardiovascular pathology either mentioned in the history or found in the pretreatment physical examination. As it is apparent from the table below the adverse events have comparable frequencies in the placebo and Circadin arms. In addition there are no differences in the kind of Adverse Events observed in patients with cardiovascular abnormalities and in patients not suffering from cardiovascular disease.

Table: Adverse Events by Cardiovascular status

	CIRCADIN				PLACEBO			
	No CV Abnormal		CV Abnormal		No CV Abnormal		CV Abnormal	
Body System / Adverse Experience	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
BODY AS A WHOLE								
Asthenia	24	3.6	18	3.0	9	1.6	15	2.5
Headache	35	5.3	31	5.2	32	5.8	40	6.6
Pain	4	0.6	17	2.8	3	0.5	10	1.6
Pain Abdominal	13	2.0	7	1.2	16	2.9	7	1.1
Pain Back	24	3.6	14	2.3	9	1.6	4	0.7
CARDIOVASCULAR								
Hypertension	0	0.0	6	1.0	1	0.2	5	0.8
DIGESTIVE								
Constipation	8	1.2	7	1.2	7	1.3	1	0.2
Diarrhea	7	1.1	9	1.5	2	0.4	13	2.1

Nausea	11	1.7	8	1.3	6	1.1	11	1.8
METABOLIC & NUTRITIONAL								
Weight Gain	7	1.1	5	0.8	8	1.4	6	1.0
MUSCULOSKELETAL								
Arthralgia	13	2.0	5	0.8	2	0.4	8	1.3
NERVOUS								
Anxiety	6	0.9	11	1.8	5	0.9	11	1.8
Dizziness	8	1.2	12	2.0	4	0.7	11	1.8
Dreams Abnormal	5	0.8	10	1.7	8	1.4	24	3.9
Migraine	9	1.4	6	1.0	5	0.9	10	1.6
Insomnia	3	0.5	7	1.2	4	0.7	5	0.8
RESPIRATORY								
Bronchitis	18	2.7	11	1.8	4	0.7	10	1.6
Cough Increase	3	0.5	7	1.2	3	0.5	6	1.0
Pharyngitis	40	6.0	22	3.7	17	3.1	10	1.6
Rhinitis	18	2.7	12	2.0	14	2.5	12	2.0
GRAND TOTAL	248	37.3	230	38.4	162	29.3	216	35.4

In addition, Neurim has reviewed the data on cardiovascular parameters on patients receiving Circadin in some of the pivotal studies, and no differences in both heart rate and blood pressure were found between baseline and treatment readings.

Patients with Nocturnal Hypertension. An additional study was sponsored by the Company in patients suffering from nocturnal hypertension (NEU BP). No safety concerns were found with Circadin upon 4-weeks treatment in nocturnal hypertensive patients.

Patients with Renal/Hepatic abnormality. No data for hepatic insufficiency exists and for patients with renal impairment the data are limited to 8 patients participating in protocol NEU 201005. From the safety analysis, it is apparent that there are no differences in total of AEs for all body systems in the subgroup of hepatic / renal impairment *vs* the total population. In addition to these data the applicant submitted one more short-term study in patients suffering from end stage renal disease being on chronic hemodialysis. In this study the major findings were that there was no Circadin accumulation in the blood between week 1 and 3 and there were no safety concerns both in lab tests and reported AEs and SAEs (none).

Patients with Diabetes. Two long-term studies of 5 months and 6 months were conducted in diabetic patients suffering from insomnia (NEU 951005, NEU 951005a). No safety concerns were found with Circadin upon long-term treatment (6-months) in diabetes type II patients.

Patients with autoimmune diseases. A number of isolated published reports suggest that melatonin has immune enhancing effect. No clinical data exists concerning the use of Circadin in individuals with autoimmune diseases. Therefore, Circadin is not recommended for the use in patients with autoimmune diseases.

Patients with Benign Prostatic Hyperplasia. A single-centre, randomised double blind, two parallel groups study of prolonged-release melatonin (5 mg, once daily) vs placebo in a 6 months treatment of patients with benign prostate hyperplasia and a 12 months extension of single blind treatment with prolonged-release melatonin was performed (Study NEU 951003). No serious adverse events were reported, no changes in vital signs (blood pressure and heart rate) and no differences in laboratory values as compared to baseline values were found.

Insomniacs discontinuing chronic use of benzodiazepines. A single centre, randomised double-blind study comparing the efficacy of melatonin prolonged release (2 mg once daily) versus placebo, in a 6 week treatment of patients complaining of insomnia and discontinuing chronic use of benzodiazepines, with 6 weeks extension period of single blind and 6 months follow up period of

Circadin treatment was performed (Study 961009). Circadin appeared to be safe even when given alone or concomitantly with benzodiazepines or during benzodiazepine withdrawal.

Pregnancy and lactation. Melatonin is present in human breast milk and may communicate time of day information to breast-fed infants. Exogenously ingested melatonin may also reach breast milk, and reflect blood concentrations of melatonin with a short delay. Although we have no evidence that melatonin has an effect on breast-fed babies, treatment in breast feeding mothers is not recommended, as reflected in the SPC.
Circadin is proposed only for use in patients of 55 years of age or over, and so reproduction toxicity and milk transfer are of little relevance to this age group.

- Safety related to drug-drug interactions and other interactions, overdose, withdrawal and dependence

Drug interactions. The applicant presented safety data (pooled AEs) from previously run studies (30424, NEURIM-I, NEURIM-IV & NEURIM-V), in patients taking or not taking concomitant medications. More specifically in this analysis the applicant includes 76 Circadin patients taking simultaneously hormone replacements, 37 taking Calcium channel blockers, 27 with beta-blockers, 28 with ACE inhibitors, 113 with NSAID, 35 with antidiabetics, 53 with benzodiazepine or Zolpidem and 20 with anticoagulants.
Conclusions cannot be drawn from so small patient numbers. For the two biggest groups (hormone replacements and NSAIDs), there are no differences observed in frequencies and kind of AEs between patients on Circadin or placebo and those taking concomitant medication.
Additional PK interaction studies were not submitted.

Previous interaction studies showed no PK interaction with 50 mg thioridazine and a possible PD interaction, no PK interaction with 75 mg imipramine or desipramine but again with a possible PD interaction.

Finally, 800 mg cimetidine increased the plasma concentration of melatonin, but not the PD response and neither the PK of cimetidine. All the studies had the same design i.e. single dose, three way crossover and the dose of Circadin was 2 mg.

Overdose. No specific cases of overdose with melatonin administration have been reported. Short term studies with high exposure at a dose level of 6.6 g/day for 35 days (3000 times the proposed dose), and long term use at doses of 300 mg of melatonin (150 times the proposed dose) and 0.5 mg norethisterone per day for four months have found no biologically significant changes in hematology and clinical chemistry values.

Withdrawal and dependence. Withdrawal effects were assessed in all of Neurim Pharmaceuticals' clinical studies except Neurim IX since, according to the scientific advice, "The CPMP agrees that potential withdrawal effects do not need to be investigated in every study."
Circadin 2 mg has a short half- life, and all ingested melatonin should be cleared within <24 hours after Circadin intake; therefore early withdrawal symptoms would be expected within this time frame. Early withdrawal (up to 48 hours) and late withdrawal symptoms were explored for safety and efficacy parameters.
Neurim have checked for potential discontinuation symptoms by examining data on the incidence of adverse events, somatic symptom scales especially designed to evaluate discontinuation symptoms (Chess-84, a scale that evaluates a list of somatic symptoms relating to the digestive system, CNS and, specifically, sleep and wake-time parameters, and Tyrer scale, which is used to record the symptoms of patients undergoing withdrawal from hypnotics), and sleep measures.
The table below summarises all this data and presents some relevant numbers.

Table: Withdrawal effects in Neurim studies: efficacy and safety parameters

Study (parameters)	**Efficacy Variables**		**Safety Variables**	
	Early Withdrawal	**Late Withdrawal**	**Early Withdrawal**	**Late Withdrawal**
Neurim I (PSG; AEs)	Sleep: SL, DWAPSO, DWAPSOP ↔ Vigilance: TRT, MRT ↑	Sleep: SL, DWAPSO, DWAPSOP ↔ Vigilance: TRT, MRT ↑	4 AEs (Circadin): 4 AEs (placebo)	4 AEs (Circadin): 4 AEs (placebo)
Neurim IV (Leeds; Diary; AEs)	QOS, GTS, AFS, BFW ↑ Sleep quality; daytime ↑		AEs: 38.7% (run-in)>35.8% (double-blind)>25.8% (withdrawal)	
Neurim V long term (Diary; Chess 84; AEs)	Sleep quality and mood during the day ↑		CHESS 84 – sleep latency- 25%, 11% related to drug at washout vs. 53% baselines; sleep maintenance - 29%, 11% related to drug at washout vs. 24% baselines; CHESS score – 1.37 (Circadin): 4.81 (Buspirone): 7.06 (Lorazepam); AEs: 43% double blind; 63% open label (12 months); 20% withdrawal 6 months; 13% withdrawal 12 months;	
Neurim VII (Leeds, Diary)	QOS, GTS, AFS, BFW ↑ Sleep quality; daytime ↑		AEs: 2 patients placebo: 1 patient Circadin	Tyrer symptoms: 66% screening>60% baseline<63% treatment> 52% withdrawal AEs: 7% baseline, 10% withdrawal Circadin; 11% withdrawal placebo
Neurim IX	Not applicable		AEs 30 days post study: Overall: 396 patients: 381 no AEs; 15 AEs 7 cases Circadin: 8 cases placebo	

↔ no change compared to baseline
↑ Better than baseline
QOS- quality of sleep; GTS – getting to sleep; AFS – Awakening from sleep; BFW – Behaviour following wakening
AEs – Adverse Events
Early withdrawal – measurements made up to 48 hours after treatment stop.

In conclusion, sleep parameters declined during withdrawal following Circadin treatment, to values that were comparable or even significantly higher (in some studies- Neurim IV) than baseline levels. There was no increase in incidence of adverse events compared to those at baseline or treatment phase at any time in the withdrawal periods. There was no increase in somatic symptoms compared to those at baseline as assessed by specially designed instruments (CHESS-84 and the Tyrer scale). Finally, among sleep or safety parameters, no evidence was found for withdrawal dependence or rebound insomnia with Circadin during early and late withdrawal, beside the re-emergence of insomnia.

Moreover, the applicant committed to perform a post-marketing withdrawal study as described in the risk management plan (follow-up measure).

- Discontinuation due to adverse events

In the Circadin group, there were 17 cases (1.3% of the safety population) of adverse events leading to discontinuation of the patient. In the placebo group there were 42 cases (3.6% of the safety population) of adverse events leading to discontinuation of the patient.

The adverse events seen in the Circadin group were insomnia, headache, anxiety, asthenia, depression, dizziness, over-sedation, abdominal pain, vomiting, paroxysmal nocturnal dyspnea, leuconeutropenia, ALT increase, bilirubin increase, GGT increase, alcoholic intoxication, skin rash, AE of the eye, and hot flushes.

The events in the placebo group were GGT increase, anxiety, headache, nausea, dizziness, malaise, sweating, diarrhoea, tremor, migraine, tachycardia, visual disorders, insomnia, myalgia, palpitations, BZD withdrawal syndrome, asthenia, drowsiness, pancreatic neoplasm, bronchitis and flu like syndrome.

The table below summarises the number of AEs causing discontinuation from the study, both per study and for the pooled data.

Table 5: Number of Discontinuations due to AEs in Neurim studies

Study	**Circadin** **N=1264**	**Placebo** **N=1163**
Neurim I	----	---
Neurim IV	9	20
Neurim V double-blind	2	1
Neurim V open label	---	
Neurim VII	---	2
Neurim VIII	4	16
Neurim IX	2	3
Total	**17 (1.3%)**	**42 (3.6%)**

Considering the two pivotal studies, 2 patients under placebo withdrew from Neurim VII study, one patient because complained day drowsiness and another due to dizziness. In Neurim IX protocol, 2 patients under Circadin withdrew because of tracheitis and over sedation, and 3 patients receiving placebo because of pressure in head & behind eyes, worsened migraine and neck pain and headaches.

- Post marketing experience

Whereas melatonin has been on the market as food supplement in several countries, there is no post marketing experience for Circadin.

- Discussion on clinical safety

The overall rate of adverse event is about 37% in Circadin and 31% in placebo groups. The most common adverse events were headache, pharyngitis back pain and asthenia with a similar frequency between Circadin and placebo groups. Dizziness, loss of consciousness, and falls were occasionally reported. Death and serious adverse events were considered to be unrelated or improbably related to the treatment with Circadin.

No additional data exist for hepatic insufficiency patients and very limited for renal insufficiency (8 patients). In both populations, use of melatonin is not recommended as reflected in the SPC.
Underlying cardiovascular diseases did not modify the safety profile of Circadin.
In conclusion, according to the available clinical results, Circadin appears to be safe and well tolerated the recommended dose and indication.

4. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for the pharmacovigilance , indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notifications of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notifications of any adverse reaction occurring either in the Community or in a third country.

Risk Management Plan

The MAA submitted a risk management plan.

The safety profile of Circadin as defined in the current application is relatively benign without many topics deserving special attentiveness.

Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Thyroid follicular cell hypertrophy	Routine pharmacovigilance activities	• Post-Marketing Reports: Following launch, Neurim will review the risk management plan if there are any spontaneous reports of thyroid follicular cell hypertrophy. If a review of cases suggests risk: • Add warning in Section 4.4 of the SmPC • List as an ADR in Section 4.8 of the SmPC • Produce educational packs for GPs
Visual disturbances	Routine pharmacovigilance activities	• Post-Marketing Reports: Following launch, Neurim will review the risk management plan if there are any spontaneous reports of visual disturbances. If a review of cases suggests risk: • Add warning in Section 4.4 of the SmPC • List as an ADR in Section 4.8 of the SmPC
Infections	Routine pharmacovigilance activities	• Post-Marketing Reports: Following launch, Neurim will review the risk management plan if there are any spontaneous reports of infections. If a review of cases suggests risk: • Add warning in Section 4.4 of the SmPC

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		• List as an ADR in Section 4.8 of the SmPC
Immune system	Routine pharmacovigilance activities	• Post-Marketing Reports: Following launch, Neurim will review the risk management plan if there are any spontaneous reports of immune system disorders. If a review of cases suggests risk: • List as an ADR in Section 4.8 of the SmPC
Drug interactions	Routine pharmacovigilance activities	• Post-Marketing Reports: Following launch, Neurim will review the risk management plan if there are any spontaneous reports of drug interactions. If a review of cases suggests risk: • Add warning in Section 4.4 of the SmPC • List as an ADR in Section 4.8 of the SmPC
Drug withdrawal	• Routine pharmacovigilance activities • A post-marketing study will examine withdrawal in the general population based on CHMP guidance	• Post-Marketing Reports: Following launch, Neurim will review the risk management plan if there are any spontaneous reports of drug withdrawal. If a review of cases suggests risk: • Add warning in Section 4.4 of the SmPC • List as an ADR in Section 4.8 of the SmPC In addition, the risk minimisation and risk communication plan will be determined when data from the post-marketing study becomes available
Loss of Consciousness	Routine pharmacovigilance activities	• Post-Marketing Reports: Following launch, Following launch, Neurim will review the risk management plan if there are any spontaneous reports of loss of consciousness. If a review of cases suggests risk: • Add warning in Section 4.4 of the SmPC • List as an ADR in Section 4.8 of the SmPC

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Additionally, the applicant will perform a post-marketing study examining withdrawal in the general population (follow-up measure)

5. Overall conclusions, risk/benefit assessment and recommendation

Quality

The Quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
At the time of the CHMP opinion, there was a minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

Non-clinical pharmacology and toxicology

The putative role of melatonin in regulating sleep and how this role is mediated remains unclear. In vitro, melatonin is described in the literature as acting at the central nervous system level possibly involving interaction with melatonin MT1 and MT2 receptor subtypes. In vivo, studies in animal looked essentially at sleep induction effects, but the results are difficult to interpret and extrapolate to humans.

The mean oral bioavailability varies from 17% to 100 % depending on the dose and the animal species. Melatonin is promptly distributed in tissues and rapidly metabolised in the liver mainly by CYP1A enzymes. The main excretion route is renal excreted as sulfo-conjugates or gluco-conjugates.

Melatonin has a low toxicity after single administration. In repeat-dose toxicity (rats and dog) effects on the liver (hypertrophy) and genital tract of male rats and female dogs were observe at exposure in large excess of the intended human exposure at therapeutic dose.

In reproductive studies, melatonin induced some toxicological effects on the embryo-foetal development in rabbits and on the postnatal developmental in rats. Therefore, the use of Circadin is not recommended during pregnancy and lactation. This is reflected in sections 4.6 and 5.3 of the SPC.

The carcinogenic potential, has not been completely elucidated in view of the thyroid findings in the rat carcinogenicity study and further mechanistic data will be provided as a post-authorisation commitment. Since no genotoxic properties have been identified for melatonin, and as the animal exposure was in large excess to the expected one in the clinic, considering also that the treatment is not proposed to be continuous for long periods, and provided that this well established mechanism of thyroid tumorigenesis in rodents can be clearly proven by the applicant (follow-up measure), the risk to humans appears to be minimal.

Efficacy

The two pivotal trials, Neurim VII and Neurim IX have shown a statistically significant effect on the rate of responders, based on both combined criteria of “quality of sleep” and “behaviour following wakefulness” with 14% difference compared to placebo in a pooled analysis (20% for Neurim VII and 11 % for Neurim IX). The effect size is recognised to be small. Comparison between zolpidem and Circadin on QOS appears to be similar in magnitude and variability, although this comparison, which is based on a separate study, is questionable.
Overall the results in the different studies accumulated in this dossier suggest that the product is efficacious with a small effect size and in a relative small fraction of patients.

Safety

From the safety database, all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

The overall rate of adverse event is about 37% in Circadin and 31% in placebo groups. The most common adverse events were headache, pharyngitis back pain and asthenia with a similar frequency between Circadin and placebo groups. Dizziness, loss of consciousness, and falls were occasionally reported. Death and serious adverse events were considered to be unrelated or improbably related to the treatment with Circadin.

No additional data exist for hepatic insufficiency patients and very limited for renal insufficiency (8 patients). In both populations, use of melatonin is not recommended as reflected in the SPC.
Underlying cardiovascular diseases did not modify the safety profile of Circadin.
In conclusion, according to the available clinical results, Circadin appears to be safe and well tolerated at the recommended dose and indication.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 of this document adequately addressed these.

- User consultation

The user test consultation, provided with the response to the list of question was satisfactory.

Risk-benefit assessment

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product and in particular for the following areas:

- Any post-marketing reports of thyroid findings. Furthermore thyroid hormone measurements will be performed in available sample from animal studies and clinical trials (follow-up measure)
- Any post-marketing reports involving any form of visual disturbance,
- Any post-marketing reports regarding loss of consciousness and related adverse event (e.g. syncope),
- The rate of infectious diseases will be periodically reviewed in the PSURs,
- The risks of withdrawal, dependence and abuse will be carefully monitored and will be subject to a careful post-marketing monitoring.

Additionally, the applicant will perform a post-marketing study examining withdrawal in the general population (follow-up measure).

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Circadin, as monotherapy, in the short-term treatment of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over, was favourable and therefore recommended the granting of the marketing authorisation.