Bibliographic documentation for application of marketing authorization for Melatonin AGB.

Modul 2.5 Clinical overview

2.5.1 Introductory remarks and product development rationale

Pharmacotherapeutic group: Melatonin Receptor Agonists, ATC-code: N05CH, more specifically Melatonin N05CH01.

The primary targeted indications are:

[redacted]

Circulating levels of melatonin vary in a daily cycle, thereby regulating the circadian rhythms of several biological functions both in animals and humans. In humans the most important circadian rhythm is the sleep-wake cycle.

Melatonin is an endogenously occurring hormone, sometimes designated the natural sleep hormone of the body, produced by the pineal gland. Endogenous melatonin production varies with age and declines during adulthood such that by age 70 years, nocturnal melatonin concentration may be less than a quarter of that seen in early adulthood. This is considered to contribute to impaired sleep in older individuals. Therefore it is thought that treatment with melatonin can substitute the age-related reduction in melatonin levels thereby restoring normal sleep patterns.

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, i.e. circadian rhythm disorders, include e.g. jet lag syndrome, shift work sleep disorder and non 24 h sleep-wake syndrome in blind people. In all these circumstances insomnia might appear as a syndrome. This is the background for treating disturbances of the sleep-wake cycle with melatonin.

Melatonin is a well-established product in EU, according to the EU Directive, [redacted] A prolonged-release formulation of melatonin containing 2 mg melatonin, Circadin, was registered by the central procedure in Europe in 2007. As this prolonged-release product is available only in the strength of 2 mg, it does not meet patients´ requirement for a fast-release product at different strengths. Thus, there is a need for a fast-release melatonin product. *Melatonin AGB* is a rapid dissolving tablet, [redacted]

[redacted] Thus, *Melatonin AGB* is aimed for the treatment of the primary targeted indications given in the current application.

[redacted]

Brief presentation of clinical tools to identify sleep disorders

To reveal sleep disturbances, there are a number of various types of questionnaires as well as sleep diaries to be used either as self-reports or records of a care giver/observer. The somnogram is such a formula to be filled in showing sleep and wake patterns over a period of time. For further evaluation polysomnography and actigraphy are used. Polysomnography includes measurements of brain activity (EEG), eye movements (electrooculogram), skeletal muscle activity (electro-myogram), heart activity (ECG), respiratory activity as judged by nasal and oral airflow, and by pulse oximetry. It follows that polysomnography is uncomfortable for the subject under examination and further, has to be carried out at a sleep laboratory. The use of an actigraphy is a simple procedure which can be used over several days and in the patient´s home. The device is watch-like ("actiwatch") and worn on the wrist of the non-dominant arm. It records gross motor movements (and also the light). Data are continually collected to be read later on a computer [redacted]

[redacted]

In the text to follow, if not otherwise stated, the type of formulation is fast/immediate release.

2.5.2 N/A

2.5.3 Overview of Clinical Pharmacology

Pharmacological properties

Kinetics

[redacted]

Bioavailability
A review [redacted] concludes that the bioavailability of oral melatonin is approximately 15%

With regard to original reports and oral intake of fast/immediate release formulations:

[redacted] report a [redacted]

Estimated first-pass metabolism
The following literature underlines an extensive first pass metabolism of melatonin:

[redacted]

Pharmacokinetic interactions

Melatonin is mainly metabolised by CYP1A enzymes. Therefore, interactions between melatonin and other drugs that affect CYP1A enzymes is possible. Due to increased knowledge of the CYP family, interactions with different CYP enzymes can now be distinguished.

[redacted]

A number of drugs induce CYP1A2 and may therefore have the potential of reducing plasma concentrations of melatonin. [redacted]

[redacted]

[redacted]

Adrenergic agonists/antagonists, opiate agonists/antagonists, antidepressants, prostaglandin inhibitors, benzodiazepines, tryptophan and alcohol affect the endogenous secretion of melatonin in the pineal gland, but do not affect the metabolism of melatonin [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The combined use of the calcium channel blocker nifedipine and melatonin may reduce the effect of nifedipine, resulting in increased blood pressure and heart rate.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.5.4 Overview of clinical efficacy

Reduction of sleep onset latency in adult patients

[redacted] was asked to provide a scientific opinion on a list of health claims pursuant to [redacted] The opinion accounted for here, addresses the scientific substantiation of a health claim in relation to melatonin and reduction of sleep onset latency [redacted]

A claim on melatonin and reduction of sleep onset latency and improvement of sleep quality has earlier been assessed by EFSA with an unfavourable outcome [redacted] based on a meta-analysis [redacted] of randomized controlled trials conducted in subjects with sleep disorders under sleep restrictions (subjects with changes in sleep pattern, e.g. after jet lag, shiftwork or induced insomnia), which did not show an effect of melatonin consumption on sleep onset latency or sleep quality.

However, three meta-analyses of controlled trials, which assessed the effect of melatonin consumption on sleep onset latency in healthy subjects without insomnia [redacted] in subjects with primary sleep disorders [redacted] or in healthy subjects with or without insomnia [redacted] were not considered in the aforementioned published opinion [redacted]

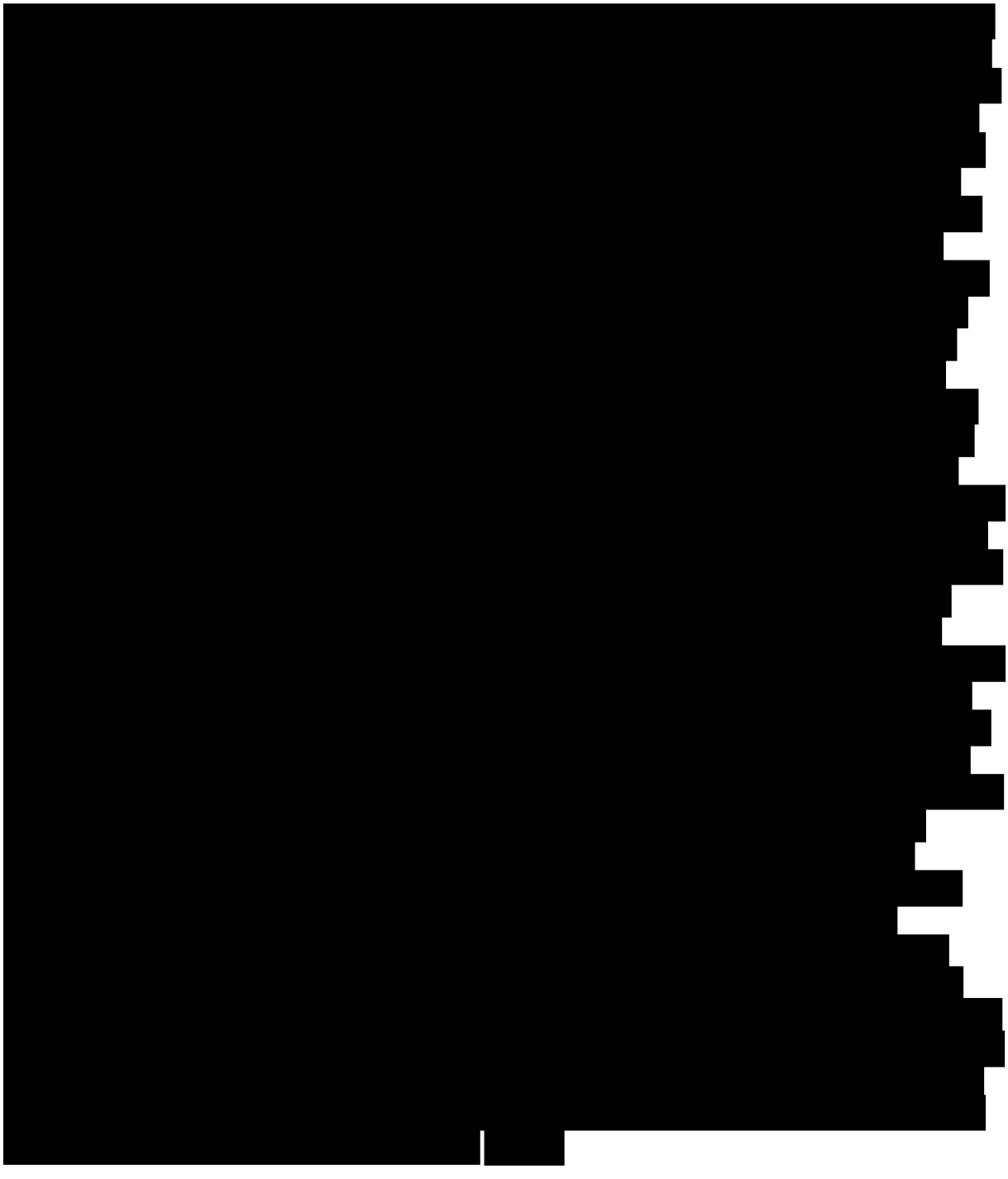
In the updated scientific opinion [redacted] the [redacted] concludes that:

"*A cause and effect relationship has been established between the consumption of melatonin and reduction of sleep onset latency.*

The following wording reflects the scientific evidence: "Melatonin helps to reduce the time to fall asleep."

In order to obtain the claimed effect, 1 mg of melatonin should be consumed close to bedtime. The target population is the general population."

[redacted]



Supportive documentation

In a recent meta-analysis *"Melatonin for the treatment of primary sleep disorders"* [redacted] the authors conclude*: "This meta-analysis demonstrates that melatonin decreases sleep onset latency, increases total sleep time and improves*

[redacted]

Alleviation of subjective feelings of jet lag in adult patients

EFSA Scientific opinion on melatonin and alleviation of subjective feelings of jet lag: Following a request from the European Commission, European Food Safety Authority (EFSA) was asked to provide a scientific opinion on a list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006. The opinion accounted for here, addresses the scientific substantiation of a health claim in relation to melatonin and alleviation of subjective feelings of jet lag [redacted]

[redacted]

In the scientific opinion [redacted] the EFSA Panel concludes that:

"The claimed effect is "sleep-wake cycle regulation". The target population is assumed to be the general population. Alleviation of subjective feelings of jet lag might be a beneficial physiological effect. A cause and effect relationship has been established between the consumption of melatonin and alleviation of subjective feelings of jet lag.

The following wording reflects the scientific evidence: "Melatonin contributes to the alleviation of subjective feelings of jet lag".

In order to bear the claim, the melatonin dose should be between 0.5 and 5 mg and should be taken close to bedtime on the first day (and any subsequent day) of travel and on the following few days after arrival at the destination. The target population is the general population."

[redacted]

[redacted]

Cochrane Systematic Review of melatonin for the prevention and treatment of jet lag: The Cochrane Systematic Review [redacted] of randomized placebo-controlled trials with melatonin interventions for alleviating jet lag had as a primary measure subjective ratings of jet lag. Among the main results accounted for in the Cochrane Systematic Review were the following (p.2): *"Daily doses of melatonin between 0.5 and 5 mg are similarly effective, except that people fall asleep faster and sleep better after 5 mg than 0.5 mg. Doses above 5 mg appear to be no more effective. The relative ineffectiveness of 2 mg slow-release melatonin suggests that a short-lived higher peak concentration of melatonin works better."*

[redacted]

[redacted]

[redacted]

Adverse effects: [redacted]

[redacted]

[redacted]

[redacted]

Melatonin treatment for children with visual impairment

Disturbed sleep patterns and complains about morning fatigue have been associated with delays in the secretory pattern of melatonin in children with severe visual impairment [redacted]

Children with visual impairment and sleep disorders are a very heterogeneous group of patients and very few randomized placebo controlled double blind studies have been performed. One study accounts for the use of melatonin to treat sleep-wake-cycle disorders in 100 visually impaired children aged three months to 17 years.
Melatonin (2.5-10 mg, 5 mg in most instances) was given orally at the desired bedtime and the children were generally asleep after 30 minutes. Within 3-4 days, the children´s sleep patterns began to improve and the improvement continued 2-4 weeks. There were no adverse side effects reported, not even morning sedation. In several children, the melatonin treatment, together with better sleep routines improved their sleep so well that in a few months the treatment was discontinued and the sleep problems did not recu[redacted]

An open study from Sweden accounts for long-term melatonin treatment in blind children and young adults with circadian sleep-wake disturbances. Melatonin, initially in the range 0.2-2 mg and later adjusted to up to 4 mg, given in the evening dramatically improved the sleep-wake pattern in all patients. The effect was maintained during long-term therapy for between 1 and 6 years in 8 patients. No side effects were noted during the therapy[redacted]

Melatonin treatment of blind adult people

Most totally blind people have circadian rhythms that are ”free-running”, i.e., that are not synchronized to environmental time cues and that oscillate on a cycle slightly longer than 24 hours. This condition is also called “non-24 h sleep/wake disorder”. The transmission of ocular light from the retina is necessary to keep the normal circadian rhythm of 24 h, which is necessary for the optimal function of the body. In a recent review it was concluded that daily administration of exogenous melatonin is the current treatment of choice for this disorder affecting the majority (76%) of subjects with no light perception. Melatonin (0.5 mg per day) was reported to correct the underlying circadian rhythm abnormality as well as improving sleep and reduce daytime napping[redacted]

Prescription of melatonin in Sweden, Denmark and Norway

In *Sweden,* statistics for the use of melatonin (regardless of formulation) has been reported between the years 2006-2016 by the National Board of Health and Welfare. The prescription database shows a gradual increase in the number of subjects using melatonin, from 3,011 in 2006 to 79,534 in 2016, the prevalence increasing from 0.33/1,000 inhabitants to 8.07/1,000 inhabitants. 129 children, aged 0-4

years, received melatonin in 2006, while in this age group the number was 834 in 2016. For children and adolescents aged 5-19 years, there was an increase in the number of users from 2,088 (in 2006) to 31.872 (in 2016); the prevalence of melatonin use, during this period, increased from 1.26/1,000 - 19.28/1,000 for these ages [redacted]

In *Denmark*, Sundhedsdatastyrelsen [redacted] covers the use of melatonin (regardless of formulation) from 2007. From their "Primærsektor", it was reported an increase of the use of melatonin for the whole population, from 485 (2007) to 53,292 (2016), corresponding to an increase in the prevalence of melatonin use from 0.09/1,000 to 9.34/1,000 inhabitants. In 2007, 5 children, aged 0-4 years, got melatonin, while the number for this age group was 331 in 2016, corresponding to an increase from 0.02/1,000 children to 1.12/1,000 children. With respect to children under 1 year of age, 3 received melatonin 2008, while the corresponding number was 16, in 2016. During 2016, 61 children 1 year of age and 77 children 2 years of age had been treated with melatonin. For children and adolescents aged 5-19 years, there was an increase in the number of users from 57 (in 2007) to 10,493 (in 2016); the prevalence of melatonin use, during this period, increased from 0.05/1,000 – 10.24/1,000 for these ages.

In *Norway*, an increase of melatonin (regardless of formulation) use in children and adolescents has been reported [redacted] the prevalence of melatonin use among subjects of 4-17 years age, increased during the period 2004–2012, in boys 3 times (from 3.4 to 11.0 per 1,000 boys) and in girls 5 times (from 1.5 to 7.7 per 1,000 girls).

2.5.5 Overview of safety

Summary of the safety profile

Melatonin causes few, and no serious adverse reactions in the short term, up to 3 months. Long-term effects are poorly studied. The most common side adverse reactions of melatonin are headache, nausea and fatigue in both adults and children. These adverse reactions are also common for placebo-treated patients in the clinical studies and no reported significant difference between patients who received active treatments and placebo is seen in these studies.

Adverse reactions of melatonin prolonged-release tablets
No common or very common side adverse reactions were reported.
Adverse reactions (uncommon) in adults who received oral treatment with melatonin 2 mg prolonged-release tablets are compiled below according to MedDRA system organ classification.

[redacted]

The following adverse reactions were reported in clinical trials and from post-marketing spontaneous reports for melatonin 2 mg prolonged-release tablets. In clinical trials a total of 9.5% of the patients receiving melatonin prolonged-release tablets reported an adverse reaction compared with 7.4% of patients taking placebo. Only those adverse reactions reported during clinical trials occurring in patients at an equivalent or greater rate than placebo have been included below.

The undesirable effects are presented within the frequency interval of the category uncommon (≥1/1,000, <1/100):

Psychiatric disorders
Uncommon: Irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety.
Nervous system disorders
Uncommon: Migraine, headache, lethargy, psychomotor hyperactivity, dizziness, somnolence.
Vascular disorders
Uncommon: Hypertension.
Gastrointestinal disorders
Uncommon: Abdominal pain, upper abdominal pain, dyspepsia, mouth ulceration, dry mouth, nausea.
Hepatobiliary disorders
Uncommon: Hyperbilirubinaemia.
Skin and subcutaneous tissue disorders
Uncommon: Dermatitis, night sweats, pruritus, rash, pruritus generalised, dry skin.
Musculoskeletal and connective tissue disorders
Uncommon: Pain in extremity.
Renal and urinary disorders
Uncommon: Glycosuria, proteinuria.
Reproductive system and breast disorders
Uncommon: Menopausal symptoms.
General disorders and administration site conditions
Uncommon: Asthenia, chest pain.
Investigations
Uncommon: Abnormal liver function test, increased weight.

<u>Paediatric population</u>
The frequencies of adverse reactions may be different in children.

The EFSA Panel considered that *"Melatonin appears to be safe with short-term use (three months or less)"* and that for treatment of jet lag the "*melatonin dose should be between 0.5 and 5 mg*". [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Use in special populations

Pregnancy and fertility

[redacted]

[redacted]

Breast feeding

[redacted]

[redacted]

Epilepsy

Melatonin has been reported to either increase, decrease or being without effect on seizure frequency. [redacted] of British

[redacted]

Immunological diseases

Melatonin seems to ameliorate some autoimmune diseases, [redacted] while it may not affect or even be detrimental for others, [redacted]

[redacted]

Elderly

There is typically an inverse relationship between age and melatonin with lower physiological plasma levels with increasing age, apparent in the range of 60-90 years, even though there are exceptions reported among some elderly persons, exhibiting high melatonin levels [redacted] The decline in plasma melatonin levels is probably not due to an increase in clearance [redacted] or to an increase in the metabolism of melatonin - in fact, as to the latter, the activity of CYP1A2 is either reduced (> 65 years, [redacted] or not affected by age (mean age 70 years vs 25 years, [redacted] A likely explanation to the decrease in plasma levels of melatonin is a decrease of its release from the pineal gland, which in turn may have various causes [redacted]

[redacted]

Children

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Overdose

[redacted]

Several cases of overdose have been reported. Somnolence was the most reported adverse event. Most were mild to moderate in severity [redacted]

[redacted]

In summary melatonin causes few and no serious [redacted] The most common side effects of melatonin are headache, fatigue and nausea. However, these side effects are also common for placebo-treated patients and there is generally no significant difference between patients who received active treatment or placebo.

The Swedish Medical Products Agency has provided the numbers of licences for the fast-release preparation Melatonin Natural Pharma in the strengths 0.5 mg, 1 mg, 2 mg, 3 mg, 4

mg and 5 mg which they have approved during the period 1998-01-01 - 2016-11-08. [redacted] During this period there was approved 3 licenses during 1998 and then there was an increase in the number of licenses from 689 in 1999 to 9,131 in 2015.
The total number of licences since 1998 has been 68,535 and the number of possible prescriptions may be 274,140 since each license may be used for four prescriptions during one year.

In Sweden, during a period of more than [redacted] a total of [redacted] adverse reactions have been registered in connection with the use of melatonin. Of these, [redacted] were considered as serious, and the majority of the patients were adults or adolescents. Eleven of these serious adverse reactions were potentially connected with the use of Circadin, one with the use of Melatonin Natural Pharma (prescribed on a named patient basis) and another one with the use of the magistral preparation *Melatonin AGB and* yet another in response to the intake of a dietary supplementum preparation; in [redacted] of the case reports, the formulation of melatonin was not stated [redacted]
The event assessed as a possible connection with Melatonin Natural Pharma, an immediate/fast release formulation, concerns a 6 year old boy with autism and an unspecified mental retardation that had been on the melatonin medication, in addition to Theralen, for about one year and reacted with quick shakings of the arms and later attacks of absence with deviation of the eyes, a limp body, fatigue and fever. The initial dose was 4 mg, which was increased to 8 mg after approximately 10 months. With respect to *Melatonin AGB,* the report was assessed as unclassifiable because of lack of documentation. A 62 year old man with bipolar disorder type 1, who also medicated with lithionit, experienced on the 9th day of treatment with 5 mg of melatonin numbness and swelling around the mouth 20 minutes after the intake; in the morning there was a clear swelling of the face as well as an angioedema.

In conclusion, in Sweden, there has been extremely few adverse reactions reported for the fast-release preparations Melatonin Natural Pharma and *Melatonin AGB*.

2.5.6 Integrated overview and conclusions

Insufficient sleep has serious consequences. Attention lapses, performance deficits, difficulties in learning and memorizing, and in the long run, metabolic and cardiovascular diseases, and increased risk of mortality. There are three main theories with respect to our need of sleep. One states that sleep is necessary to restore energy resources of the body. A second theory is related to the immune-defence system - sleep is thought to boost the immune system and to promote the recovery of the body from infections. The third theory underlines the need of sleep for consolidating the memory where both the REM (rapid-eye-movement) sleep and the non-REM sleep are of importance and further, sleep maintains synaptic homeostasis, i.e. during waking synapses are formed and during sleep they decrease in number. Sleep consists of two main alternating phases, displaying 4-5 cycles. Sleep begins with a period of non-REM sleep characterized by reduced heart rate and fall in blood pressure, and reduced respiratory frequency and fall in core temperature. During the following period of REM sleep the skeletal muscles lose their tone (apart from the respiratory muscles and those skeletal muscles that are innervated by the cranial nerves). Moreover, the

heart rate, blood pressure and breathing are irregular. During the non-REM sleep, the electroencephalography (EEG) shows the amplitude of the EEG-waves ("delta" waves) to increase and the frequency to decrease, while the EEG-waves of the REM sleep and waking are characterized by low-amplitude and high frequency ("theta" waves). The REM sleep is associated with dreams (mainly based on a review by [redacted]

Though the included data of the present literature are not always consistent with respect to the three parameters, time of onset of sleep, duration of sleep and quality of sleep, the overall conclusion - as judged from a large number of publications - must be that melatonin is an effective drug for the treatment of sleep disorders and particularly for those involving de-synchronization of the circadian rhythm. The effect of melatonin is modest but on the other hand hang-over and addiction to the drug as seen in connection with the use of more potent sleep-promoting drugs are lacking. The daily melatonin dose range is [redacted] and [redacted] In that dose range, reported side effects are rare, being of the same frequency and nature as those reported for placebo. [redacted] was without effect on vital signs and a battery of laboratory tests; somnolence and headache were reported but did not differ in frequency from those to placebo [redacted] Importantly, the melatonin treatment did not change the architecture of sleep. [redacted] oreover, benzodiazepines and benzodiazepine related drugs, e.g. zopiclone and zolpidem are associated with impaired [redacted] while this is not the case with melatonin at a dose of 10 mg [redacted]

Attention should be paid to interactions between melatonin and [redacted] A prolonged-release formulation of melatonin at a dose of 2 mg administered in the evening to healthy subjects (aged 55 years and older) does not affect psychomotor functions, memory recall, and driving skills (using a simulator) assessed at 1 hour and 4 hours post-administration, and the next morning. In contrast the short-acting drug [redacted] at a dose of 10 mg impaired psychomotor and driving performance as well as memory recall at the early post-dosing stages; at the next morning the memory recall was still impaired. The prolonged-release melatonin (2 mg) potentiated the effect of [redacted] since the impairments to [redacted] shown at the early stages and the memory recall decline at the late stage were enhanced. The authors refer the potentiation to CNS-GABA-effects rather than to pharmacokinetic effects, a conclusion that gains support from the in vitro observation on human hepatic preparations that [redacted] does not impair the metabolism of melatonin [redacted]

The safety margin appears wide with respect to melatonin not only when applied in high mg-doses but also in gram-doses and over long periods of time, as pointed out in the above quoted literatures (e.g., [redacted]

Importantly, in patients suffering from [redacted] chronic melatonin treatment [redacted] improved the subjectively

experienced quality of sleep, reduced sleep latency, increased sleep duration and decreased daytime and sleep disturbances, while the [redacted] were unchanged (with the exception of [redacted] - but this was the same as in response to placebo). This observation on humans may be compared with a single non-clinical chronic study on [redacted] which reported melatonin to strengthen the [redacted] but without affecting relaxatory evoked responses and, as a consequence of the results, questioned the use of melatonin in [redacted] patients [redacted] In response to the acute exposition to melatonin non-clinical findings both in vivo and in vitro were in agreement with the [redacted] assessments of the clinical study.

[redacted]

Conclusion

As judged from the literature of both the non-clinical and the clinical studies, melatonin in the oral dose-range [redacted] can be recommended to treat the targeted indications in the application, [redacted]

Available data suggest that melatonin is also a well-tolerated and efficacious treatment option for [redacted]

The use of melatonin is, for the time being, not recommended for pregnant women, women planning a pregnancy and for lactating women. Likewise, patients with hepatic impairment or immunological diseases are not recommended for the treatment with melatonin. Caution should be taken with melatonin treatment in patients with renal impairment and in those with epilepsy. Moreover, the combination of melatonin with anticoagulants, benzodiazepine related drugs or the antidepressant fluvoxamine should, based on our present knowledge, be avoided. Particular attention should, in general, be given to those situations where melatonin is combined with drugs that exert strong inhibitory action on the melatonin metabolizing enzyme CYP1A2, such a drug is fluvoxamine; among this type of drugs may also be found calcium channel blockers as witnessed by verapamil and nifedipine, even though the

mechanism behind the elevated melatonin levels in response to the latter drug is not completely clarified. Eventually, in the light of what has been mentioned previously, individual dosing of melatonin to the elderly may be relevant.

[redacted] 02-04-2017

[redacted]

Redacted according to Section 40, FOI Act

2.5.7 List of Literature References

Redacted according to Section 41, FOI Act

Redacted according to Section 43, FOI Act

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