LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Melatonin AGB
(melatonin)

SE/H/2048/01-05/MR
Asp no: 2017-0394, 2017-0395, 2017-0396, 2017-0397, 2017-0398

This module reflects the scientific discussion for the approval of Melatonin AGB. The procedure was finalised on 2019-12-11. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

AGB-Pharma AB has applied for a marketing authorisation for Melatonin AGB, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, tablet. The active substance is melatonin (Melatonin is involved in the control of the circadian rhythm and the alignment to light/darkness cycle of the environment. Melatonin, at least at somewhat higher doses, also has a mild hypnotic effect.)

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Introduction

No new non-clinical studies with melatonin have been conducted, which is acceptable. The non-clinical part of the application is bibliographic.

III.2 Pharmacology

Melatonin is an endogenous hormone produced in the pineal gland. Melatonin exerts its biological effect by binding to the membrane bound MT1 and MT2 receptors. Both receptor types are located in the suprachiasmatic nucleus, whereas only MT1 receptors are found on the pituitary pars tuberalis. MT1 receptors are involved in the regulation of retinal function, circadian rhythms and reproduction.

Both in humans and in the experimental animals, the pineal gland secretion of melatonin is high during the dark cycle. Most studies on the effect of melatonin on the wake/sleep cycle have been performed on nocturnal animals such as rats and mice, i.e. species that are active during the night, in contrast to the humans. Only few observations have been made on animals (*i.e.* monkeys) displaying a distinct diurnal cycle like humans. The difference in day/night activity between humans and rodents concomitant with a similar pattern of melatonin secretion (low in light/high in dark) make comparisons between diurnal and nocturnal species difficult. Moreover, it should be recognized that melatonin may act on other structures and functions than just the suprachiasmatic nucleus and its circadian rhythm to exert its effect on sleep; e.g. the propensity for sleep may be associated with a decrease in the core body temperature and a peripheral vasodilatation, and with an enhancement of inhibitory transmission mechanisms (GABA) or a decrease of excitatory mechanisms (glutamate) in the CNS.

In rats, there are reports favoring the idea that melatonin causes earlier onset of sleep and an extension of the sleep time, but there are also reports that do not support these conclusions. In the crepuscular cat, the sleep onset time is earlier and, in some experiments, the sleep time is prolonged. In the monkey, sleep onset time is shortened and sleep time increased. Obviously, and apart from species chosen, the dose used and the time of administration are factors of importance for the sleep response. It may be noted that melatonin just affects the rhythm of the suprachiasmatic nucleus when administered at a certain time of the day, i.e. at dusk. Eventually, it must be concluded, that the results of the experimental studies are still insufficient to provide detailed information about the effect of melatonin on the sleep process, and that extrapolation to explain the established melatonin evoked sleep response in humans must be made with caution.

Melatonin has effects on several hormones involved in the sexual maturation of pubertal female and male rats.

III.3 Pharmacokinetics

Melatonin is rapidly absorbed from the gastrointestinal tract within one hour after administration.

The bioavailability is moderate in rats (53%) and high in dogs and monkeys (100%) upon oral administration of melatonin.

Melatonin binds to albumin (78%) according to the in vitro observations; a similar figure (80%) is valid for humans. The hormone is distributed within 1-2 minutes. The elimination half-live of the hormone is short, 19.8 minutes in rats, 18.6 minutes in dogs and 33.9 minutes in monkeys.

Melatonin crosses the placental barrier. Melatonin is rapidly metabolized by the liver, mainly by CYP1A2 and, in addition, by CYP2C19; in the mouse 95% is metabolized within 30 minutes. The main metabolite is sulphate conjugate 6-hydroxymelatonin (70-80%), while 6-hydroxymelatonin glucuronide is a minor metabolite (5%) with respect to the rat (and humans). In contrast, in mice the main metabolite is 6-hydroxymelatonin glucuronide (75-88%). The excretion is via the urine (60-70%) and faeces (15%, after 48 hours).

III.4 Toxicology

Single-dose toxicity
The single dose toxicity of melatonin after oral administration is low.

Repeat-dose toxicity
The section on repeat-dose toxicity is very limited. The poor information of repeat-dose toxicity is considered acceptable based on the WEU legal basis of application.

Genotoxicity
The genotoxicity of melatonin has been evaluated although not fully in agreement with the recommendations in ICH S2 (R1). Applicant has provided references from a number of genotoxic studies. Concluded from these studies are that melatonin does not possess any mutagenic nor clastogenic effects. In the light of the fact that melatonin is an endogenously produced molecule, and that the available literature does not point to any mutagenic or genotoxic effect, it is agreed that melatonin does not present any significant genotoxic potential.

Carcinogenicity
A few long-term studies of melatonin are included in the dossier. While none of these studies can be accepted as formal carcinogenicity studies (less than life-time exposure, few parameters investigated, dose and exposure data are lacking, poor documentation), the studies indicate that melatonin administration may increase survival in rodents.
In conclusion, in the available literature, there are no indications of melatonin being either genotoxic or carcinogenic in experimental animals.
Thus, the absence of formal carcinogenicity studies is considered acceptable.

Reproductive and developmental toxicity
Fertility and early embryonic development
The limited robust non-clinical information on potential effects of melatonin on male and female fertility may be justified by availability of clinical data. The effects of melatonin on different hormones in men and women have been investigated in several studies.

Embryo-foetal development
An embryo-foetal development study in rats revealed no adverse effects at dose levels higher than the maximum recommended dose.
The absence of adequate embryo-foetal development data in non-rodents is considered acceptable.

Pre-and postnatal development
The absence of solid pre-and postnatal development data is considered acceptable.

Juvenile toxicity
No formal juvenile studies have been presented. As requested, the Applicant has provided a literature review on the potential effects of melatonin during juvenile development. The cited

literature indicate that melatonin delays the onset of puberty in animals. It is known that endogenous melatonin levels are high in prepubertal children and is dramatically reduced during puberty. This suggests that administration of exogenous melatonin leading to supraphysiological levels in pre-pubertal and pubertal children may potentially lead to pubertal abnormalities. This theoretical concern has somewhat been supported by the fact that melatonin is involved in the hormonal control of seasonally breeding animals. However, as most data are obtained in seasonal breeders the relevance to humans is unclear.

III.5 Ecotoxicity/environmental risk assessment

As melatonin is an endogenous molecule, Melatonin AGB is not expected to present any potential risk to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

The endogenous hormone melatonin is currently primarily used off-label in the treatment of sleep disturbances in children with neuropsychiatric or neurodevelopmental disturbances. This application relies on published data and the Applicant hasn't performed any clinical studies on their own.

IV.2 Pharmacokinetics

No clinical PK studies have been performed using the proposed product, Melatonin AGB. Only published literature references using different melatonin doses and formulations were provided to support the present application.

Absorption

The absolute bioavailability of melatonin is reported to be in the order of 15%. Melatonin undergoes extensive first-pass metabolism.

The impact of food intake on melatonin's PK is unclear. Limited literature references and high variability in data are pointing towards an increase in melatonin's exposure under the fed conditions. Dose-linearity was demonstrated across different clinical PK studies for melatonin's exposure (expressed as both AUC and Cmax) with administered doses of up to 10 mg.

Distribution

Plasma protein binding in vitro is about 60% (fu = 40%).

Elimination

The mean elimination half-life is reported to vary between 30-60 min. About 90% of an oral dose was eliminated in the urine mainly as metabolites, only <1% was excreted unchanged.

Melatonin is metabolised primarily via CYP1A2 enzyme, with certain contributions from CYP1A1 and CYP2C19 enzymes. Some *in vitro* data also implied potential involvement of extrahepatic enzyme CYP1B1 in the metabolism of melatonin.
Following an oral dose of 14C-melantonin, 6-OH-sulphate, 6 OH-glucuronide and 6-OH-melatonin were identified in the urine to ≥60%, ≥21% and ≥2% of the dose, respectively.

Special populations

Renal and hepatic impairment
Decreased renal function is not expected to influence the elimination of melatonin as <1% of the dose is excreted unchanged in the urine following an oral dose. However, no clinical studies with melatonin in renally impaired patients are available/presented.

Melatonin is mainly eliminated via liver metabolism, and therefore an effect of liver impairment on melatonins exposure is expected. However, no clinical studies with melatonin in hepatically imapaired patients are available/presented.

Gender
In one clinical study a 3-fold higher Cmax has been observed in females compared to male subjects after an oral dose of melatonin. However, in the same study a very high inter-individual variability for this parameter was also observed, especially between female subjects, which makes it difficult to draw conclusions about the gender differences and its potential impact on melatonin PK.

Age
Systemic exposure of endogenous melatonin decreases with age, however whether this happens due to decreased release from the pineal gland or increased elimination is unknown. On the other hand, in one clinical study it appeared that exogenous administration of melatonin tended to result in a higher and more variable exposure in elderly compared to younger people.

Interactions
In general, all perpetrator drugs that are affecting CYP enzymes which are involved in melatonin's metabolism (CYP1A2 and/or CYP2C19) could potentially affect melatonin's exposure with or without potential clinical consequences. On the other hand, there is a limited data available in terms of melatonin as a perpetrator of pharmacokinetic interactions.

A 17-fold higher total exposure of melatonin was seen when co-administered with fluvoxamine compared when administered alone. Fluvoxamine is a known strong inhibitor of both CYP1A2 and CYP2C19. thus the involvement of CYP2C19 in the elimination of melatonin cannot be ruled out.The systemic exposure of melatonin increased 4- to 5-fold in subjects using oral contraceptives containing ethinyl-estradiol compared to subjects not using oral contraception. Ethinylestradiol has been reported to inhibit CYP1A2.
The total systemic exposure of endogenous and administered melatonin was ca 2-fold higher following caffeine intake. The inhibitory effect was more pronounced in non-smokers compared smokers. Caffeine is a known CYP1A2 inhibitor.

Discussion on pharmacokinetics

This application is primarily based on bibliographic data on melatonin.

As melatonin can be generally considered as a substance belonging to the I class of BCS, and since Melatonin AGB showed comparable *in vitro* dissolution results to other approved melatonin IR products (see also Quality section), it is agreed that clinical data generated with simple IR formulations of melatonin can be considered applicable to Melatoning AGB. Therefore, the question about the comparative bioavailability is considered resolved.

There were very limited literature data presented by the Applicant in order to support proposed dosing in paediatric population (and to justify different starting doses in children under and over 7 years of age). In addition, a very limited number of study subjects, as well as high inter-

individual variability, represent a significant limitation for making conclusions about the pharmacokinetics of melatonin in children. Therefore, from the pharmacokinetic point of view, presented literature data are considered insufficient to provide basis for optimal dosing recommendations in paediatric population. However, since the proposed dosing of the current product will be effect driven (dose is adjusted on the individual basis with the aim to find the lowest effective dose; maximum daily dose set to 5 mg), the clinical assessment appears more relevant in terms of evaluation of the proposed dosing rather than the PK assessment.

Finally, additional PK information were provided by the Applicant in the form of literature references concerning plasma protein binding, volume of distribution, metabolic pathways, pharmacokinetic interactions, time-dependency, inter-individual variability, age and gender influence on melatonin's PK, etc. Therefore, further updates of the SmPC based on these literature resources were performed.

In summary, presented basic PK data from the literature are considered sufficient to provide adequate support for basic melatonin's SmPC information.

IV.3 Pharmacodynamics

Primary pharmacology
With respect to sleep, melatonin has two major effects. It induces sleep and it phase-shifts the circadian rhythm. The effect of exogenous melatonin is a question of timing.

Sleep propensity. The role of melatonin is thought to inhibit wakefulness-producing activity and to accelerate the secretion of melatonin. The administration of melatonin makes use of a positive feedback mechanism enhancing its own release. About 2 hours before habitual bedtime, melatonin secretion begins to increase. This secretion is thought to gate the opening of the nocturnal sleep gate occurring about 100 min after the onset of melatonin secretion. To be effective as a sleep inducer, melatonin, administered orally, should be given about 30-60 min before bed-time, allowing time for melatonin to become bioavailable. The nocturnal gate opening is a rapid event.

Phase shift of the circadian rhythm: the chronobiotic effect. Depending on the time of administration exogenous melatonin may influence the circadian clock. When given during the so-called phase advance zone, i.e. late afternoon, particularly 3-4 hours (some say 4-5 hours) before the beginning of the nocturnal rise of melatonin, the circadian clock phase-advances. When given in the late night/early morning, ± 1 hour around the usual offset of endogenous melatonin secretion, the phase is delayed. Taken in the middle of the day, melatonin is without its phase-shifting effect and thus, there is no meaningful clinical result.

Delayed sleep phase syndrome. The person suffering from the delayed sleep phase disorder goes to bed and wakes up more than two hours later than at conventional times. The sleep pattern, is however, stable. A fixed dose, usually 5 mg but also lower doses (0.3-1.0 mg), given in the early evening, at the same clock time, for 2-6 weeks, has been found effective.

Secondary pharmacology

Prolonged treatment of children with melatonin is controversial, due to its reported effects on the reproduction of animals, where usually seasonal breeders have been studied.

Onset of puberty in humans has been associated with a marked fall in nocturnal melatonin., However, no data on a potential relation between the reduction in melatonin levels in children and effects on sexual hormones, sexual maturation or growth is currently at hand.The association of melatonin with pubertal development may be the product of maturation of the neuroendocrine-gonadal axis, rather than reflecting a regulatory role of melatonin.

Relationship between plasma concentration and effect
No data presented by the applicant on the relationship between plasma concentration and effect.

However, the relation between plasma concentration and effect may not be so relevant for melatonin, since it exerts its main effects on the circadian rhythm and sleep in certain areas of the brain and the local concentrations needed in the brain is probably not directly related to the plasma concentrations.

Discussion on pharmacodynamics

The applicant has presented a summary on the primary pharmacology of melatonin, which is needed for the understanding of the role of melatonin in the regulation of the circadian rhythm.

The applicant has presented a summary of relevant secondary pharmacology related to effects on hormones, including sexual hormones and sexual maturation/pubertal development in children, metabolic effects related to insulin and the regulation of blood glucose levels.
No data presented by the applicant on the relationship between plasma concentration and effect. However, the relation between plasma concentration and effect may not be so relevant for melatonin, since it exerts its main effects on the circadian rhythm and sleep in certain areas of the brain and the local concentrations needed in the brain is probably not directly related to the plasma concentrations.

Conclusions on pharmacodynamics
The applicant has provided relevant data on pharmacodynamics.

IV.4 Clinical efficacy

The legal ground for the application has been evaluated by the MPA for each indication, separately (in line with the *Annex I of Directive 2001/83/EC*). The evaluation is presented below.

Indication 1: Short term treatment of jet lag in adults.

Two tablet formulations containing the active substance melatonin have been in well-established use within the Community for at least 10 years as “authorized medicinal products”.

Indication 2: Insomnia in children and adolescents aged 6 17 years with ADHD, where sleep hygiene measures have been insufficient.

MPA assessment of the legal ground:
The favourable effects of melatonin for the jet-lag indication can be agreed upon.

The favourable effects of melatonin for the paediatric indication of children and adolescents with ADHD is considered proven based on the prescription data for the last decade or more, showing an increasing prescription to children, primarily those with ADHD as comorbidity and several scientific reports and clinical treatment guidelines.

Conclusions on the legal ground
In summary, the legal ground is considered supported for the indications jet-lag and Sleep disturbances and circadian rhythm disorders in children and adolescents with ADHD.

Clinical efficacy

Indication 1: Impaired rhythm of sleep and wakefulness in adults, due to disturbance of the biological circadian rhythm (e.g. jet-lag).

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 (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2010).
In the scientific opinion (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2010, p.7-8), 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.”
Further The EFSA Panel considered that “Melatonin appears to be safe with short-term use (three months or less)”. (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2010, p.7).

Cochrane Systematic Review of melatonin for the prevention and treatment of jet lag:
The Cochrane Systematic Review 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.”
The conclusions of the Cochrane Systematic Review were (p.2): “Melatonin is remarkably effective in preventing or reducing jet lag, and occasional short-term use appears to be safe.”

Indication 2: Sleep disturbances and circadian rhythm disorders in children and adolescents with ADHD.

As many as 70% of children with ADHD have been reported as having mild to severe sleep problems. The causes of sleep onset insomnia in children with ADHD are likely to be heterogeneous and multifactorial.

Main study

Study Design and Conduct
This was a A 4-week randomized, double-blind, placebo-controlled study, immediately following a 1-week baseline period. Participants were randomly assigned (1:1 ratio) to receive melatonin, 3 mg when body weight <40 kg [n = 44]; 6 mg when body weight >40 kg [n = 9]) in fast-release tablets or identical-appearing placebo tablets at 7:00 PM.
Subjects

107 children were enrolled in the study. Inclusion criteria included 6 to 12 years old, diagnosis of ADHD and SOI.. Main exclusion criteria were total IQ <80, epilepsy, earlier use of melatonin, and use of stimulants, hypnotics, or beta-blockers within 4 weeks before enrolment.

Outcome Measures
Sleep was estimated using actigraphy and sleep logs., Primary sleep outcome parameters were sleep onset, total time asleep, and sleep log item difficulty falling asleep.

RESULTS
Of 107 patients, 105 received melatonin (n = 53) or placebo (n = 52). At baseline, there were no significant between-group differences in demographic variables, clinical characteristics..

Efficacy Measures

Sleep
There was an increase in mean total time asleep of 19.8 ± 61.9 minutes with melatonin and a decrease of 13.6 ± 50.6 minutes with placebo (p = .01). As compared with placebo, the melatonin group showed a significant decrease in sleep latency (p=.001), increase in sleep efficiency (p=.01) and decrease of nocturnal restlessness (L5; p = .03).

Long-term follow-up study
This was a long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia who participated in the main study. It was a questionnaire-based study which included responses from 94 of the original 105 children with a mean FU of 3.66 years. The dose range was 0.5 to 10 mg. Sixty-five percent of the children still used melatonin daily and 12% occasionally. Temporal discontinuation of treatment (in 67/94) resulted in a delay of sleep onset in 92% of the children. Nine percent of the children could discontinue melatonin completely because of improvement of sleep onset insomnia. Three children discontinued the treatment
because of adverse events.. In 2 children, the physician discontinued treatment because of concerns regarding the effects of long term treatment on pubertal development, but details are not given.

Supportive study

This study investigated the effects of 5 mg melatonin in a placebo-controlled cross-over study (duration of treatment period 10 days) in 22 stimulant-treated children with ADHD and insomnia who were non-responders to sleep hygiene measures. 19 subjects provided results. The initial sleep hygiene measures decreased sleep latency from a mean 91.7 min to 69.3 min.. After 10 days treatment, mean sleep latency was 62.1 ± 26.6 min on placebo and 46.4 ± 26.4 min on melatonin (p<0.01). No daytime function measures were collected. 17 subjects were considered melatonin responders and continued melatonin for an additional 3 months open-label treatment. At the end of this 3 months period, their mean sleep latency was 31 min.
The study showed aa significant reduction in initial insomnia of 16 minutes with melatonin relative to placebo.. Adverse events were generally mild and not different from those recorded with placebo treatment. Improved sleep had no effect on ADHD symptoms.

<u>Discussion on efficacy</u>

Fulfilment of WEU criteria

The WEU relevant criteria have been fulfilled for the indications jet-lag in adults and sleep disturbance in children and adolescents with ADHD.

Efficacy discussion

The jet-lag indication
Several publications have been presented, enabling the conclusion that melatonin has proven effective in ameliorating the subjective symptoms of jet-lag.

Children and adolescents with ADHD and sleep disturbance.
Studies of sufficient size studying the effects of melatonin in a selected population of children with ADHD and insomnia have been presented by the applicant. Thus, the ADHD indication is considered approvable.

The main study
Children with sleep onset insomnia and ADHD were selected for this study. Diagnostic criteria for ADHD and insomnia are well described and appear appropriate for the study goal.

The placebo-controlled treatment period was only 4 weeks, which may be insufficient in duration for the chronobiotic effect of melatonin to emerge. However, the dose was in the dose range for a hypnotic effect of melatonin to occur as well.

The outcome measures appear appropriate for a study on insomnia. The EMA insomnia guidelines state that efficacy should be demonstrated not only on sleep parameters but also on daytime performance. Daytime performance was measured as a rating of each child's core problem, selected based on the reports from the parents and teachers. In addition, several aspects of cognition and QoL were measured.

The statistical methods are overall well described for being a publication.
Sleep latency was shortened from 53.0 ± 22.0 min at baseline by 21.3 ±33.0 min by melatonin, and slightly lengthened from 47.3 ± 23.2 min at baseline by placebo (+3.0 ±31.7 min). A shortened sleep latency is often considered clinically relevant, if the mean treatment difference from baseline is in the range of 20-30 min (e.g. Slenyto SmPC). The total sleep time (baseline 519 min) was slightly increased by melatonin by around 20 min, but this increase is not considered clinically relevant.

The endpoints related to daytime functioning were overall not significantly affected by melatonin treatment.

The overall impression from this clinical study was that it was well-designed, of border-line size and, of short duration. The results demonstrate a clinically relevant effect on sleep latency. However, these effects on sleep don't translate into clinically relevant effects on daytime function. This is similar to the case of Slenyto, a recently approved slow-release melatonin, which also mainly failed to show positive effects on daytime functioning in children with ASD and insomnia.

The follow-up study was a questionnaire-based long-term FU of the main study. The study provides some further data that melatonin was used daily for a prolonged period by the majority of children. 2 children were discontinued by the treating physician because of concerns regarding the effects of long term treatment on pubertal development. Unfortunately, no more details are given in the publication.

The supportive study is considered to give some further support to the effect of melatonin on sleep latency.

Dosing in children
Different doses have been used in the clinical trials referred to, however, the doses were most often between 1-10 mg taken before bedtime. In the main study fixed doses of were used. A flexible dosing strategy is considered more appropriate for the use of melatonin in children and adolescents.

Age cut-off for melatonin in children with ADHD
All approved ADHD medications (methylphenidate, dexamphetamine, lisdexamphetamine, atomoxetine) are approved from 6 years of age and ADHD is often not diagnosed before the age of 6 years. Accordingly, MPA considers that the lower age cut-off for the indication treatment of sleep problems in children with ADHD should be 6 years.

Conclusions on efficacy
The relevant criteria have been fulfilled for the indications jet-lag in adults and sleep disturbance in children and adolescents with ADHD.

The MPA considers the efficacy data for the jet-lag and sleep disturbance in children and adolescents with ADHD are of sufficient quality to be approved.

IV.5 Clinical safety

Adverse events
The Tabulated list of ADRs is almost identical* to the SmPC for Bio-Melatonin, which has been licensed in Hungary since 2003. It is also almost identical* to that of Circadin, centrally approved in EMA since 2007.

*=The only ADR added for melatonin AGB is “hallucinations” with the frequency “unknown”. This is based on 5 case reports of hallucinations and one of delusions. It is also noted that for other commonly used sleep-inducing medications (e.g. zopiclone, zolpidem, nitrazepam, flunitrazepam), both hallucinations and delusions (or similar wordings) are listed as ADRs in 4.8.The undesirable effects are presented within the frequency interval of the category uncommon (≥1/1,000, <1/100) or unknown:

Psychiatric disorders
Uncommon: Irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety.
*Unknown**:** Hallucinations*
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.

Paediatric population
The frequencies of adverse reactions may be different in children.

Overdose
Melatonin displays a wide safety margin. High daily doses of melatonin have been used in ranging from 20 mg to 300 mg without any adverse effects**.** Even a prolonged intake of melatonin 1 g (i.e. 250 mg x 4) per day was without toxicity**.**

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

Laboratory findings
Melatonin 10 mg per day for 4 weeks in healthy subjects 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**.**

Safety in special populations
Epilepsy
Melatonin has been reported to either increase, decrease or being without effect on seizure frequency.

A review article concludes that there is a paucity of relevant data from a remarkably small number of studies of which some suggested worsening of seizures and others indicated improvement of seizure control with melatonin allowing no firm conclusions to be made.
Immunological diseases
Melatonin seems to ameliorate some autoimmune diseases, while it may not affect or even be detrimental for others.

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. The decline in plasma melatonin levels is probably not due to an increase in clearance or to an increase in the metabolism of melatonin - in fact, as to the latter, the activity of CYP1A2 is either reduced (> 65 years) or not affected by age (mean age 70 years vs 25 years. 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**.**

Discussion on safety

The tabulated list of ADRs is identical to that of Bio-Melatonin, approved in Hungary. This is acceptable. During the procedure, the ADR of “hallucinations” was added to the psychiatric ADRs with the frequency unknown. This was based on 5 case reports of hallucinations and 1 of delusions.

From non-clinical data on seasonal breeders and the observation that plasma concentrations of melatonin rapidly decline around puberty, there is a theoretical concern that long-term treatment with melatonin may affect sexual hormones, sexual maturation/pubertal development and final height in children and adolescents. To this end, the Applicant has agreed on performing a PASS study, using the Swedish prescription registry and the Swedish patient registry.

Robust data on the long-term safety of treatment with melatonin in children and adolescents is still lacking.

Conclusions on safety
Since most publications on the effects of melatonin focus on the efficacy of melatonin in various disorders, safety data are scarce. From the limited data presented on safety, Melatonin appears safe when used as a short-term treatment for adult insomnia and sleep disturbance in children and adolescents with neuropsychiatric disorders. However, the long-term safety in children and the possible effects on pubertal development are not known.

IV.6 Risk Management Plans

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Melatonin AGB.

Summary table of safety concerns:

Important identified risks	None
Important potential risks	• Long-term safety in children and adolescents • Effects on sexual maturation in children
Missing information	None

Summary of the Pharmacovigilance Plan
In summary, routine pharmacovigilance is considered appropriate for all safety concerns listed above.

Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan:

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Deadline for submission of protocol synopsis to MPA
Post-authorisation safety study (PASS) on long-term safety in prepubertal and pubertal children (Non-interventional, 3)	To investigate long-term safety in prepubertal and pubertal children, considering the theoretical concern of effects of long-term melatonin treatment on hormones and sexual maturation.	Sexual maturation in children.	Planned	May 2020

The Applicant has committed to submit the protocol synopsis including well-defined endpoints for the planned PASS study and a feasibility assessment of the planned study to the MPA for our review within 6 months from the approval.

Summary table of risk minimisation measures:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Long-term safety in children and adolescents	Proposed text in SmPC: Section 4.2 "Posology and method of administration". Prescription only medicine.	A post-authorisation safety study (PASS) on long-term safety in prepubertal and pubertal children.
Effects on sexual maturation in children	Proposed text in SmPC: Section 4.2 "Posology and method of administration". Prescription only medicine.	A post-authorisation safety study (PASS) on long-term safety in prepubertal and pubertal children.

Summary of the RMP
The submitted Risk Management Plan, version 1.0 signed Oct 11 2019 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the MPA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk

profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was Swedish.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The favourable effects of melatonin have been established for the jet-lag indication in adults and on sleep latency in children with ADHD and sleep problems.

The short-term unfavourable effects are mild and well established, since melatonin has been used for decades as an OTC product in the US. The long-term safety in children and adolescents is not well described and there are concerns that melatonin may affect the growth and/or pubertal development. The applicant has committed to design a safety post-authorisation study (PASS) on long-term safety in prepubertal and pubertal children, considering the theoretical concern of effects of long-term melatonin treatment on sexual maturation and growth. The protocol synopsis and a feasibility assessment of this PASS should be submitted to MPA for our approval within 6 months from this approval.

The benefit-risk is considered positive for the indications “shot-term treatment of jet-lag in adults” and “sleep disturbances and circadian rhythm disturbances in children and adolescents 6-17 years with ADHD where sleep hygiene measures have been insufficient” and Melatonin AGB, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, tablet is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

Post approval commitments

Description	**Due date**
The protocol synopsis including well-defined endpoints for the planned PASS study and a feasibility assessment of the planned study should be submitted to the MPA for our review.	Within 6 months from approval date

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Melatonin AGB, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, tablet was approved in the national procedure on 2019-12-11.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/2048/01-05/MR	Initial mutual recognition procedure	-	2020-05-08	Approval	N/A

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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