LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Melatonin AGB Pharma
(melatonin)

SE/H/2310/01-06/DC

This module reflects the scientific discussion for the approval of Melatonin AGB Pharma. The procedure was finalised on 2023-10-24. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Melatonin AGB Pharma, 0,5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, tablet.

The active substance is melatonin. A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Melatonin AGB Pharma, 0,5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, tablet, is submitted according to 10a of Directive 2001/83/EC. The applicant, AGB-Pharma AB, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, NO as concerned member states (CMS).

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

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. There is data that indicates that melatonin has other ways of influencing sleep/circadian rhythm; 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 (i.e., GABA) or a decrease of excitatory mechanisms (i.e., glutamate) in the CNS.

The clinical effect of melatonin is well-established. While non-clinical in vivo data generally support this, many of these studies have been conducted in nocturnal animals, making the relevance to humans uncertain. However, there is also evidence from primates that shows similar sleep-inducing effects as observed in humans.

Data presented regarding primary pharmacology is considered acceptable. Melatonin has effects on several hormones involved in the sexual maturation of pubertal female and male rats.

Pharmacokinetics
Bioavailability is moderate in rats (53%) and high in dogs and monkeys (100%) when melatonin is administered orally. In comparison, the bioavailability of melatonin in humans shows a large variation but is overall lower than the previously mentioned animal species.

Melatonin binds to moderately to albumin in rat blood, ~80%. A similar figure is observed in humans. Circulating melatonin is rapidly distributed into various tissues, including the brain. Melatonin is distributed within one to two minutes and the elimination half-life is short, about 20-35 minutes in rat, dog, and monkey.

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 the 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 major metabolite is 6 hydroxymelatonin glucuronide (75-88%).

The excretion is via the urine (60-70%) and faeces (15%). These data highlight the kidneys as the main elimination route.

The provided information on melatonin pharmacokinetics is generally acceptable, given the well-established nature of this product. However, some basic absorption related PK parameters are still warranted.

Toxicology

General toxicity

Data from rodent studies indicate low acute toxicity of melatonin. Since there is no exposure data from these rodent studies it is difficult to exactly determine the exposure margins to human exposure. It is nevertheless concluded that the margins are large. Repeated dosing for 28 days, s.c. administration of melatonin to adult rats at dose levels up to 4.8 mg/kg (males) and 7.3 mg/kg (females) per day showed neither death nor effects on body weight, haematology, clinical chemistry, gross pathology or in organ weights. After infusion of 3% melatonin two out of 10 males had decreased testicular weights and degenerative changes composed of reduced or absent spermatogenesis and oedema. In another study daily s.c. injections of up to 4.8 mg/kg for 30 days to rats was without any effects on the reproductive organs. Interestingly, higher doses of 8 mg/kg had effects on male reproductive organs by reducing prostate weights. Summarizing the general toxicity data, melatonin shows low toxicological potency.

Genotoxicity and carcinogenicity

From the outcome of several tests (bacterial reverse test, in vitro Comet assay, in vitro chromosome aberration test, and in vivo mammalian micronuclear test), it can be concluded that melatonin itself exerts neither mutagenic nor clastogenic effects. In addition, investigations indicate that melatonin has anti-mutagenic potential in vivo. Although the presented publications do not fully cover the recommendations in ICH S2 (R1), the applicant has conducted a thorough literature review on the genotoxic potential of melatonin and a good summary of its results. In the light of melatonin being 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.

No formal carcinogenic study has been presented. A few long-term studies were described by the Applicant in the dossier. For example, in a transgenic mouse model expressing breast cancer associated oncogene, melatonin delayed the appearance of tumours and reduced the incidence of tumours. Other studies that are not dedicated carcinogenicity studies have been presented; however, these studies point at a protective effect rather than cancer promoting effect. While none of the submitted long-term studies can be accepted as formal carcinogenicity studies (less than life-time exposure, few parameters investigated, dose and exposure data is lacking, poor documentation), the studies indicate that melatonin administration may increase survival in rodents. Nevertheless, the fact that melatonin is an endogenously produced molecule, and that the available literature does not point to any mutagenic or genotoxic effect, the absence of formal carcinogenicity studies is acceptable.

Reproductive toxicology

No formal fertility study has been presented. Some data is however presented by the applicant indicating beneficial effects of melatonin on female fertility decline in terms of delaying ovarian ageing. Male fertility, in terms of inhibited testicular development and reduced weight of testes, have been reported in rats at doses above 4.8 mg/kg. At a dose of 0.1 mg/kg melatonin administered for 8 weeks to Sprague Dawley rats, no effects on sperm count or motility were seen. 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 state of evidence is adequately reflected in the SmPC. Thus, the information provided on fertility is acceptable.

In rats, there are observations showing that litter size and offspring are affected by high exogenous doses of melatonin given during pregnancy in terms of reduced birth weight and body weight gain at high dose (100 mg/kg) of melatonin to the dams. In a GLP study, which is deemed robust in terms of design and quality, melatonin was administered by oral gavage at doses of 0, 50, 100 and 200 mg/kg/day. Mild maternal toxicity seen as a transient reduction in body weight gain was noted at 200 mg/kg/day, and the maternal NOAEL was 100 mg/kg/day, corresponding to a HED of 16 mg/kg/day. Melatonin had no effect on the number of corpus lutea, implantations, live fetuses, preimplantation loss, resorptions, weight or sex ratio of the fetuses, nor did melatonin affect any of the end-points related to embryo-fetal growth, viability, or morphological development. Thus, the developmental NOAEL in this study was ≥ 200 mg/kg/day, corresponding to a HED of 32 mg/kg/day. The maximum recommended daily dose for the indications sought for in this MAA is 5 mg, corresponding to 0.1

mg/kg/day in a 50 kg patient. Thus, the information provided on embryo-foetal development is acceptable.

Published formal nonclinical studies on potential effects of melatonin on pre- and postnatal development are limited and the implications of the findings for humans are uncertain. Available data in rodents indicate effects on birthweight and gonadal development, whereas in cows, body weight gain was seen in calves of melatonin treated dams. However, for the time being, melatonin is not recommended to women during pregnancy or lactation, which is adequately stated in the SmPC. Furthermore, data on placental and lactational transfer of melatonin is also adequately reflected in SmPC. Thus, the information provided on prenatal and postnatal development is acceptable.

There are indications from nonclinical data that exogenous melatonin could alter timing of sexual maturation. 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. From a nonclinical perspective, information presented is sufficient concerning juvenile animals.

In summary, the nonclinical toxicology section of the provided dossier is acceptable.

Environmental Risk Assessment (ERA)
Since Melatonin is an endogenous substance, it is not expected to pose any significant risk to the environment. The provided ERA is acceptable.

IV. CLINICAL ASPECTS

Pharmacokinetics
No clinical pharmacokinetic (PK) studies have been performed using the proposed melatonin product. Only published literature studies/articles using different melatonin strengths and formulations were provided to support the present marketing authorisation application of melatonin regarding its PK properties.

Absorption
The oral bioavailability of melatonin is generally in the range of 10-35%, but as low as 3% have been reported in some clinical studies. The low and variable bioavailability is largely related to the extensive first-pass metabolism of melatonin. In one clinical study with high variability and limited number of study subjects (i.e., 4-5 study subjects per drug formulation) about a 2-fold higher exposure of melatonin was observed when administered together with food compared to fasting conditions. However, these data are considered too limited to describe the exact magnitude of food impact on PK parameters of melatonin and its potential clinical relevance.

Distribution
Plasma protein binding *in vitro* is about 60% (i.e., fu = 40%). Volume of distribution during the terminal elimination phase is reported about 1 L/kg.

Elimination
The mean elimination half-life is reported to vary between 30 - 60 min. Less than 1% of a melatonin dose is excreted unchanged in urine.

Melatonin is metabolised primarily via CYP1A2 enzyme, with some contributions from CYP1A1 and CYP2C19 enzymes.

Special populations
Decreased renal function is not expected to influence the elimination of melatonin since <1% of the dose is excreted unchanged in the urine following an oral dose. The metabolites of melatonin are mainly eliminated renally and may accumulate.

Melatonin is mainly eliminated *via* liver metabolism and an effect of liver impairment on the PK of melatonin is expected. Cirrhotic patients have been shown to have higher exposure than healthy subjects.

In a single clinical study, a 3-fold higher exposure has been seen in females compared to male subjects after an oral dose of melatonin. However, in the same study a very high inter-individual variability was observed which makes it difficult to draw conclusions about the gender differences and its potential impact on melatonin's PK.

The mean peak melatonin serum levels after melatonin treatment tended to be higher and significantly more variable in elderly subjects than among the younger subjects.

Limited information about the PK data in children has been provided by the Applicant, in general melatonin appear to have a comparable in children and adolescents as in adults.

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.

Other CYP1A2 inhibitors also increases melatonin exposures e.g., 5-or 8-methoxypsoralen, cimetidine, oestrogens and caffeine.

CYP1A2 inducers such as carbamazepine and cigarette smoking may decrease melatonin levels.

Discussion on pharmacokinetics
This is an application according to Article 10a well-established use (WEU), which is primarily based on bibliographic data on melatonin. As this is a complete application, the bibliography should cover all aspects of pharmacokinetics needed to make a complete characterisation of the disposition of the compound. For a WEU application, establishing a link between the applied for product and the literature data used to support efficacy and safety is considered crucial. The Applicant has provided a bridging discussion as well as in vitro dissolution data which is considered sufficient.

The basic pharmacokinetic parameters of melatonin are generally described by the Applicant.

Pharmacodynamics
Melatonin is an endogenously occurring hormone produced by the pineal gland, sometimes designated as the natural sleep hormone of the body. Melatonin belongs to the pharmacotherapeutic group: Hypnotics and sedatives, melatonin receptor agonists, ATC code: N05CH01. The suprachiasmatic nucleus (SCN) contains neurons that exhibit a circadian pattern of activity and regulate melatonin secretion by the pineal gland in response to the environmental light/dark cycle. Under normal conditions, the activity of the SCN is entrained to the 24-hour cycle: it is reset on a daily basis by light during the day and by melatonin during the night. The circadian influences of the SCN on the body functions are mediated via nerves and hormones, particularly by circulating melatonin.

Mechanism of action and primary pharmacology
Melatonin exerts its effect via various subtypes of melatonin receptors such as MT1 and MT2 receptors in the human central nervous system (CNS). Melatonin receptors also occur in a number of human tissues outside the CNS, e.g., in the cardiovascular system, immunological systems and the digestive tract (Ekmekcioglu 2006).
Exogenous melatonin has both sleep-inducing and chronobiotic effects. About two hours before habitual bedtime, melatonin starts to increase. To induce sleep in the evening, oral melatonin should be given 30-60 min before bedtime.

Clinical efficacy

The applicant has applied for the following two indications, which in turn are stated in section 4.1 of the SmPC document:

- "**Short term treatment of jet lag in adults**" and
- "**Insomnia in children and adolescents aged 6-17 years with ADHD when sleep hygienic efforts have not been sufficient**".

The proposed indications are accepted.

Short term treatment of jet lag in adults
The Applicant has submitted 11 scientific publications with double-blind, randomized, placebo-controlled clinical studies to support the indication *Short term treatment of jet lag in adults*. Two of these studies can be considered as pivotal for the efficacy claims of melatonin in the applied indication. Two studies were negative and did not show a significant effect of melatonin on jet lag. The remaining studies were of lower quality and are considered to be supportive for the short term treatment of jet lag in adults.
The two pivotal studies had appropriate study sizes and compared the effect of melatonin with placebo of an active comparator i.e., slow-release melatonin or zoldipem. In the two pivotal studies, subjective endpoints were used measuring sleep latency, sleep quality, sleepiness and mood states.
The results showed that that fast release formulation of melatonin was more effective compared to placebo to reduce symptoms of jet lag and it was concluded that the low dose of 0.5 mg was almost as effective as the higher dose of 5.0 mg. When compared to zolpidem, melatonin showed an effect on jet lag symtoms, while zolpidem was the most effective treatment.

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

The Applicant submitted 4 scientific publications with double-blind, randomized, placebo-controlled clinical studies. Two of these studies can be seen as pivotal. The results of the larger study showed a significant effect by melatonin on the primary endpoints in children between 6 and 12 years old who are not taking any ADHD medication. No significant effects were seen on the clinically relevant daytime function. The study had a sufficient study size, was well-designed and can be considered pivotal for an indication for children and adolescents from 6 years and older with ADHD. The smaller study also showed a significant effect by melatonin on sleep.

The two additional RCT's provides limited evidence for the applied indication due to having few children included with ADHD in one of the studies and the other did not show significant effects.

Overall conclusions on clinical efficacy
The literature studies submitted including supporting data in Cochrane review are sufficient to support the proposed indications of short-term treatment of jet lag in adults and insomnia in children and adolescents aged 6-17 years with ADHD. The SmPC is acceptable.

Clinical safety
Melatonin is a hormone produced in the pineal gland involved in controlling the circadian rhythm and adaptation to the light-dark cycle. The Applicant presented a safety overview focusing on safety aspects of exogenously administered melatonin although normal physiological processes of melatonin which are related to safety aspects (e.g., pubertal development) were also discussed. Moreover, the Applicant presented safety results obtained in the submitted clinical studies, including findings discussed in review papers for the indications jet lag in adults and for insomnia in children and adolescents with ADHD. Furthermore, sections on the long-term safety of melatonin as well as post-marketing information were included.

The short-term unfavourable effects of melatonin are mild and well established and the Applicant provided a summary about the known effects.

The Applicant has presented patient exposure data and the exposure per proposed indication for the different studies included in the dossier.

The adverse events from the different clinical studies included in the application has been described and summarized sufficiently. Furthermore, the Applicant has presented the results from a search for serious adverse events in Eudravigilance for melatonin for the years 2021 and 2022 and a list of individual case safety reports from March 2021 to January 2023.

Overall conclusions on clinical safety
The short-term unfavourable effects of melatonin are generally mild and well established. However, data for long-term safety and safety in special populations for melatonin are not extensive.

There is a theoretical safety concern of the effects of long-term melatonin treatment on hormones, sexual maturation and height, which currently is under investigation by the Applicant as part of the RMP for Melatonin AGB®.

Risk Management Plan
The MAH has submitted a revised 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 Pharma.

Safety specification
Summary table of proposed safety concerns (RMP Part II: Module SVIII).

Table SVIII.1: Summary of safety concerns

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

Pharmacovigilance Plan
AGB-Pharma AB will perform a long-term retrospective post-authorisation registry study (PASS) to investigate safety in children and adolescents with ADHD.

Risk minimisation measures
Apart from the long-term retrospective post-authorisation registry study (PASS), as detailed in the submitted RMP, routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly. The submitted Risk Management Plan, version 1.0 dated 04 October 2023, 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 RMS;
- 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

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Melatonin AGB 1 mg, 2 mg, 3 mg, 4 mg, 5 mg tablets, SE/H/2048/01-05/MR.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The applicant has applied for the following two indications:

"Short term treatment of jet lag in adults" and
"Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient".

To support these two indications the applicant has submitted literature data consisting of 12 published studies for jet lag (among which 11 were randomized, double-blind, placebo-controlled studies) and 6 published studies for children and adolescents with ADHD (among which 4 were randomized, double-blind, placebo-controlled studies). This is considered acceptable.

The maximum dose of melatonin is 5 mg for short-term treatment of jet lag in adults as well as in the treatment of insomnia in children and adolescents with ADHD. The intended indications as well as the

proposed posology are acceptable. Overall, there are no objections to approval of Melatonin AGB Pharma from a clinical point of view.

The quality aspects of Melatonin AGB Pharma (melatonin) tablets (0.5-5 mg) are acceptable.

The revised product information (SmPC / PL) is considered acceptable.

The benefit/risk ratio of Melatonin AGB Pharma, tablet, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, is deemed positive.

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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Melatonin AGB Pharma, 0,5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, tablet, was positively finalised on 2023-10-24.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

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