LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Aritonin
(melatonin)

SE/H/2638/003-004/MR

This module reflects the scientific discussion for the approval of Aritonin. The procedure was finalised on 2022-12-23. 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 Aritonin, 4 mg, 5 mg, film-coated 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 is an extension, addition of a new strength, of the previously authorised products: Aritonin, 2 mg and 3 mg, film-coated tablets. The line extension application is grouped with variations and change of legal status for the already authorised strengths.

The application for Aritonin, 4 mg, 5 mg, film-coated tablets, is an application submitted according to Article 10a of Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

For an application according to Article 10a, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

The active substance is not considered a new active substance.

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 synthesised from serotonin by arylalkylamine N-acetyltransferase (AANAT) to form N-acetylserotonin which is methylated to the final product, melatonin. Melatonin is predominantly produced by the pineal gland which is controlled by the suprachiasmatic nuclei (SCN) in the hypothalamus. The synthesis is dependent on the photoperiod phase and synchronized with the light-dark cycle via the retino-hypothalamic tract. Thus, high levels of melatonin are produced after dark onset and lowered in the early daylight hours. The primary function of melatonin is to regulate circadian biological rhythms, neuroendocrine rhythms and body temperature cycles through its action on MT1 and MT2 G protein-coupled receptors.

Pharmacology studies in non-human primates have shown that melatonin induce an earlier sleep on-set and a prolonged sleep duration with no shift of the circadian phases.

A number of studies have presented other positive effects by melatonin where most of them appear to be reliant on antioxidant activity. In addition, melatonin has been suggested to stabilise the membrane fluidity which is essential for cell functions.

Exogenous administrated melatonin has been shown to delay the puberty on-set in seasonally bred ewes and in Djungarian hamsters. This was also confirmed by pinealectomy in ewe lambs.

Administration of melatonin up to 800 mg/kg did not exert any acute toxicological effects in mice (administration route and plasma exposure is not mentioned). Cardiovascular effects have been studied in baboon and rat without any severe adverse events occurring. Reported findings were bradycardia, increased cardiac output and ventricular ejection fraction in baboons (0.3-0.4 mg/kg IV) and dose related fall in mean arterial pressure, heart rate and serotonin release in rat (30-60 mg/kg IV) while no effect were observed on these parameters in rat after an IV dosage of 5 and 15 mg/kg.

To summarize, the safety pharmacology did not point out any severe adverse events. This is acceptable for this well-established used product since the clinical safety profile is well-known.
Pharmacokinetics
Absorption - The oral bioavailability of melatonin was 53.5% in rats and > 100% in dogs and monkeys.

Distribution - *in vitro* plasma protein binding of melatonin is approximately 50 – 75%, mainly to albumin and to some extent to α_1-acid glycoprotein. The steady-state volume of distribution of melatonin in three species (rat, dog and monkeys) ranged from 1.05 to 1.48 L/kg, indicating moderate tissue distribution of melatonin in these species. In another study, the distribution of [^{14}C]-melatonin after IV administration to rat was studied in the plasma, cerebrospinal fluid (CSF), and brain. The volume of distribution and the clearance (CL) were 1.736 ± 349 mL/kg and 25.1 ± 1.7 mL/min/kg respectively. The maximum concentration in CSF was observed at 5 minutes, indicating a rapid distribution over the blood brain barrier and the [^{14}C]-melatonin concentration was 3.8 times higher in brain compared to CSF already after 2 minutes. The plasma/CSF concentration ratio was 0.38 at steady state (0.5 hours).

Metabolism - Melatonin is mainly metabolised in the liver. The isozymes CYP1A1, CYP1A2 and CYP2C19 are the main enzymes involved in the hepatic metabolism of melatonin, where CYP1A2 is the most important enzyme in the hydroxylation step, forming 6-hydroxymelatonin. 6-Hydroxymelatonin is then conjugated with sulphate and, to a lesser extent, with glucuronic acid, and the formed conjugates are mainly excreted in urine.

Excretion - The half-life of melatonin following i.v. dose of 3 mg/kg was 19.8, 18.6, and 34.2 min in rats, dogs, and monkeys respectively. The elimination half-life of melatonin in humans has been reported to be 40-50 min, suggesting a longer half-life of melatonin in primates compared to other investigated species.

In summary, the pivotal parts of the pharmacokinetics of melatonin have been adequately described. It appears that the pharmacokinetics of melatonin is well known, well studied, and sufficiently described for a well-established use marketing application according to Article 10a of Directive 2001/83/EC.

Toxicology
No repeat-dose toxicity studies have been presented by applicant. However, given the well-established use and the well-known safety profile of melatonin, the lack of such data is acceptable.

Genotoxicity

Melatonin did not exhibit any mutagenicity when bacterial reverse mutation tests was performed at concentrations of up to 5 mg/plate in either the presence or absence of an S9 activation system in any of the bacterial strains used (Salmonella typhimurium TA97, TA98, and TA100).

In vivo micronucleus test was performed in bone marrow and peripheral blood cells in rat in order to study the influence by melatonin on LPS-induced genotoxicity. Micronuclei (MN) formation increased after LPS administration in control animals, however, melatonin administration in addition to LPS treatment in rats was shown to reduce MN formation in peripheral blood as well as bone marrow cells.

In addition, in vivo mammalian micronucleus test investigated in paraquat-induced mice showed that melatonin inhibited paraquat-related genotoxicity by approximately 50% at 48 and 72 hours. These effects are, suggested by authors, likely due to melatonin’s antioxidant activity.

In yet another study, it was shown that exogenous melatonin has a protective effect in terms of genotoxicity induced by cypermethrin, in dams and their offspring when dams were exposed daily to this pesticide during pregnancy. However, the protective property of melatonin on genotoxicity seemed to be lacking in genotoxicity caused by another pesticide, methomyl.

Carcinogenicity

It is currently not possible to conclude the carcinogenic potential of melatonin in the provided non-clinical dossier. Since melatonin is endogenously produced and not suspected to possess

any mutagenic or genotoxic effects, the likelihood for melatonin to exhibit a potential to induce cancer is low.

Fertility and early embryonic development

No non-clinical information on potential effects of melatonin on male and female fertility are provided. This may be justified by the availability of clinical data and is considered acceptable since the limited available information is reflected in the SmPC section 4.6.

Melatonin had no effect on prenatal survival, foetal body weight, or incidences of foetal malformations/variations. A slight maternal toxicity was observed by reduced maternal weight gain at ≥ 100 mg/kg bw/day. Maternal NOAEL and LOAEL was 100 and 200 mg/kg/day, respectively.

Embryo-foetal development

The embryo-foetal development study in rats reported by Jahnke et al. (1999) is considered a robust study in terms of design and quality. This is a NTP study conducted in agreement with FDA GLP guidelines and considered acceptable, and the developmental toxicity NOAEL was ≥200 mg/kg/day.

Prenatal and postnatal development, including maternal function

Indian Palm squirrels where administrated with melatonin 20 µg from late gestation and during the lactation period. Pups were investigated for neonatal growth and sexual maturation. Reduced body weight was observed for both sexes. Findings such as reduced tissue weight of testis and vas deferens and decreased plasma level of testosterone was reported in male pups. In female pups, decreased weight of ovaries and uterus was observed while plasma oestradiol increased, and progesterone decreased.

A study in rat showed a retarded sexual maturation of female offspring (delayed vaginal opening) after subcutaneous administration of melatonin of 250µg/100g b.w. /day to females from the first day of pregnancy.

In mice given either melatonin implants or afternoon injections (25 µg i.p.), sexual maturation was delayed. Male pups exhibited smaller testes at 6, 8, 10, and 12 week of age and lower testes and seminal vesicle weights compared with saline-injected mice.

Chronic daily injections of melatonin seem to exhibit potential to depress reproductive function in hamsters, and that the effect is dependent on the time of day at which they are administered. The results indicate that if exogenous melatonin is administered in such a way that they add to the peak of endogenous production, there are signs that gonadal development is affected. Furthermore, excess of melatonin seems to inhibits the reproductive behaviour of male rats.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

No juvenile studies have been presented in the application. Among the proposed therapeutic indications are Insomnia in children and adolescents 6 - 17 years with attention deficit hyperactivity disorder (ADHD). As discussed in sections II.2. and IV.5.3, it is reported that exogenously administered melatonin may delay sexual development in animals. Applicant has

provided precautions in the SmPC section 5.3 regarding incomplete toxicological data in juvenile animals. This is considered acceptable.

Conclusion on toxicology

The applicant has covered the toxicological literature in a satisfactorily manner. They summarize literature showing that acute toxicity studies performed in rat and mice revealed no special hazard for humans, neither do the long-term studies in rodents. These studies provide sufficient data from repeated dose toxicity of melatonin given the well-established use and the well-known safety profile of melatonin. The applicant has also presented both in vitro and in vivo data on exogenous melatonin and its effect on genotoxicity; these data rather point to a protective effect than a potential risk. The existing knowledge suffices and is adequate for the requirements of the marketing application rooted from the Article 10a of Directive 2001/83/EC. Reproductive and developmental studies show a large safety margin to clinical exposures. The relevant information related to the influence of melatonin on gonadal maturation has been adequately reflected in the SmPC.

Thus, it is agreed that the toxicological literature provided by the applicant show that melatonin can be safely used in humans according to conditions specified in the SmPC.

Environmental Risk Assessment (ERA)

A justification for not submitting an environmental risk assessment has been provided by applicant and is presented above. It is agreed that this product will not increase the exposure to the environment since it will replace existing products on the market.

IV. CLINICAL ASPECTS

Pharmacokinetics

No new pharmacokinetic data has been presented for this extension application for 4 mg and 5 mg tablets. In the previous application for 2 mg and 3 mg tablets, the basic pharmacokinetic parameters of melatonin were adequately described using appropriate literature data, and a pilot bioequivalence study was presented as supportive data to justify clinical bridging to literature. The pharmacokinetic information and study results are shortly summarised below for reference.

Absorption

The absolute bioavailability of melatonin is reported to be approximately 15% in literature and varies between 1-56%. Despite its relatively low aqueous solubility, melatonin is classified as highly soluble in accordance with the Biopharmaceutics Classification System (BCS) due to the low tablet strength. It is completely absorbed when administered orally, although the absolute bioavailability is only 15% due to the 85% first pass effect. Hence, the drug is commonly classified as BCS Class I.

The pilot bioequivalence study

A pilot bioequivalence study using the proposed product is included in the application as supportive data. AUC and C_{max} were compared for the test and a reference product. Due to large intrasubject variability for C_{max} bioequivalence could not be concluded for the two formulations.

Linearity

Dose-linear pharmacokinetics have been described for melatonin in the range of 0.1-10 mg.

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.

Pharmacokinetic conclusion
This is an extension application with a legal ground Article 10a (well-established use). For a WEU application establishing a link between the applied for product and the literature data used to support efficacy and safety is crucial. In the original application the PK bridge to the literature was considered acceptable even though the C_{max} was outside the conventional acceptance criteria in the pilot BE study. This conclusion took into account the BCS class of melatonin, the wide therapeutic window, the clinical pharmacokinetic features of melatonin (high variability) and the need for individual titration of the dose.

Melatonin appears to have linear pharmacokinetics over the range of 0.1 - 10 mg and is generally considered to belong to BCS Class I. BCS Class I drugs are highly absorbed and have neither solubility nor permeability limited absorption. Therefore, they generally represent a low risk group of compounds in terms of the potential for excipients to affect absorption. The new strengths of 4 mg and 5 mg film-coated tablets have the same qualitiative composition as the 2 mg and 3 mg strengths and are quantitatively proportional.

Taken together, the absence of studies for the 4 mg and 5 mg strengths is acceptable from a pharmacokinetic perspective.

Clinical efficacy and safety
The current application is an extension application for addition of the new strengths 4 mg and 5 mg to the authorized Aritonin (2 mg and 3 mg), approved for the below indications with a dose range between 1-5 mg:

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

The SmPC section 4.2 Aritonin remains unchanged. Proposed changes will only effect sections 1, 2 and 3, where the additional 2 doses are included after the previous 2 doses.

The new strengths (4 mg and 5 mg) are within the approved dose range, thus the new strengths will not supersede the currently approved maximum dose for approved indications.

Addition of 4 mg and 5 mg allows for individualized and tailored dosing as well as fine adjustments of dose.

From a clinical perspective the proposed new range of strengths adds flexibility of clinical relevance for both adult subjects utilizing short-term treatment of jet-lag as well as treating insomnia in children and adolescents 6-17 years with ADHD where sleep hygiene measures have been insufficient.

Risk Management Plan
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 Aritonin.

Safety specification
A summary of safety concerns was included. No changes were proposed, and this is acceptable.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 2.0 signed 16.12.2021 is considered acceptable. No changes were proposed, and this is acceptable.

An updated RMP should be submitted:

- At the request of the Swedish 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 applicant has performed a bridging test for the strengths 4 and 5 mg (incl. OTC). The MPA have assessed this bridging test as valid for both the RX and the OTC leaflet. 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 leaflet (SE/H/2048/01-05/MR) and Aritonin 2 mg and 3 mg filmcoated tablets (5.4.1-2020-83812). This is considered acceptable.

In addition, the applicant has submitted a focus test concerning the OTC parts of the OTC PL to demonstrate that the posology was clear enough for OTC use. The focus test was found acceptable, and readability was shown. The focus test is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality part of the dossier is acceptable. No major objections regarding quality were identified. A shelf life of 2 years with no temperature storage restriction is acceptable for the 4 mg and 5 mg strengths.

The clinical and non-clinical part of the dossier is acceptable. There are no objections to approval of Aritonin, from a non-clinical and clinical point of view.

The product information is acceptable.

The benefit/risk is considered positive, and the application is therefore recommended for approval.

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

Aritonin, 4 mg and 5 mg, film-coated tablets, were approved in the national procedure on 2022-12-23.

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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
SE/H/2638/001-004/MR	Initial Mutual Recognition Procedure	Yes	2025-01-07	Approval	N/A

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

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