LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Melatonin Evolan
(melatonin)

2020-0200

This module reflects the scientific discussion for the approval of Melatonin Evolan. The procedure was finalised on 2022-07-01. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Melatonin Evolan, 1 mg/ml, Oral solution.

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 Evolan, 1 mg/ml, oral solution, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, Evolan Pharma AB, applies for marketing authorisation through the 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
Serum melatonin levels was found to decrease by 80% in mice from the age of 12 months to 27 months. The melatonin metabolite, 6- hydroxymelatonin sulfate, were higher than free melatonin in all tissues tested and was highest in cerebral cortex followed by the serum, heart, kidney, and liver. It is well-known that melatonin is decreasing with age and that treatment with exogenous melatonin may be helpful in elderly.

No pre-clinical safety pharmacology has been discussed by applicant other than what is presented under secondary pharmacology where most findings are reliant on antioxidant activity such as various poisoning situations and anti-oxidant effect on lung tissue in association to diabetes. This deficiency can be acceptable provided that the clinical safety profile is well-known and that the statement well-established use is valid for the suggested dosage in human as well as for the proposed indications.

Applicant have provided a thorough discussion on primary pharmacodynamics supported by available literature references showing mechanism of action, circadian rhythm in mammals as well as the sleep promoting effects. Melatonin is the main regulator of the biological clock located within the suprachiasmatic nucleus (SCN) and regulates the near 24 hr oscillations in neuroendocrine function, sleep-wake circadian rhythm. Since the night physiological surge of melatonin is involved in the regulation of sleep, including the sleep onset latency and duration, a number of studies in animals and men have been performed to support the use of exogenous melatonin in presence of sleep alterations.

Pharmacokinetics
Pharmacokinetic parameters were studied in rats, dogs and monkeys after intravenous and oral administration. The oral bioavailability was 53.5% in rats while dogs and monkeys exhibited an oral bioavailability of >100%.

A study in beagle dogs revealed a C_{max} of 1.15 ng/mL at 1.33 hours (T_{max}) Total plasma exposure was 3.57 ng*h/mL ($AUC_{0\text{-}inf}$).

Toxicology

Single dose toxicity
Melatonin, as a natural occurring hormone, possess low toxicity risk. Among the reported symptoms in single-dose toxicity studies were sedation, lethargy and vasodilatation demonstrated as redness of ears and limbs and decrease muscle tension, restriction of motor activity, ataxia. Symptoms such as tendon reflexes, decreased body temperature and respiratory depression was observed at the highest doses preceding death.

The reported symptoms were observed at very high dose levels with an exposure in large excess of what can be achieved in human with the proposed clinical dosage. This is considered acceptable.

Repeated dose toxicity

The repeated dose toxicity section is limited to studies investigating the life prolongation effect in mice and rats. A life prolongation for mice receiving a daily dose of 10 µg melatonin prior the dark cycle from the age of 15 months was observed. Likewise, a 16-month oral administration of melatonin to adult CD rats increased the number of rats (87%) surviving up to the age of 27-29 months while only 43% of control rats reached the same age, which was in accordance with the life expectancy.

Genotoxicity

The genotoxicity of melatonin has been evaluated in in vitro reverse mutant assay and in Single Cell Gel Electrophoresis. These tests suggest that melatonin does not exert a mutagenic effect.

Carcinogenicity

The effect of melatonin on the initiation of N-nitroso-N-methylurea (NMU)-induced carcinogenesis has been investigated. The animals were administered with melatonin two days before and one day after the NMU administration in tap water between 6 p.m. and 9 a.m. The dosage and regime were chosen for providing a rhythmical pattern of serum melatonin, known to be onco-suppressive. A dose-related response by melatonin against NMU-induced clastogenicity was observed (Musatov S.A. et al., 1998).

No formal carcinogenic studies have been performed on melatonin. 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 rather low.

Reproductive and developmental toxicity

Fertility and early embryonic development

A study using a mouse model of ovarian aging in order to assess whether long-term melatonin treatment could counteract age-associated infertility has been presented by Applicant. In this study melatonin treatment was found to increase the average number of pups, from aged mice (14-16 months old) compared to age-matched controls. In addition, an increase in pool of follicles, telomere length as well as oocyte quantity and quality were observed. Authors speculates that melatonin treatment suppressed ovarian mitochondrial oxidative damage. Another study presented by Applicant provides evidence that melatonin may enhance the success rate of *in vitro* fertilization (IVF) in mice.

In addition, a study on male mice was performed to assess male fertility in association to acetylsalicylic acid (ASA) treatment. ASA treatment resulted in a decrease in sperm parameters (parameters such as sperm count, motility and morphology and sperm chromatin dispersion, SCD), as well as serum testosterone levels and total antioxidant activity (TAC). Treatment with melatonin together with ASA increased epididymal sperm parameters and increased serum testosterone and TAC levels compared to the ASA-treated group.

Embryo-foetal development

The embryo-foetal development study in rats is considered a robust study in terms of design and quality. Aversion to treatment was initiated at 50 mg/kg, followed by reduced maternal weight gain when the dose was escalated to 150 mg/kg. At 200 mg/kg, mild sedation, reduced maternal food intake, and reduced body weight gain was observed. 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, and the developmental toxicity NOAEL was ≥200 mg/kg/day.

Pre-and post-natal development studies

No prenatal and postnatal developmental studies have been submitted by applicant. It is well-known from the literature that melatonin controls the reproductive cycle in many mammals. In addition, it is known that melatonin may exert endocrinological effects which could potentially affect puberty and

fertility in offspring. Applicant have updated the toxicology section with information on embryofoetal development and reproduction as well as endocrinological effects in mammals with accurate references. Effects regarding delay of sexual maturation has not been discussed. Since effects on nocturnal animals may not be representative for human, this is acceptable.

Environmental Risk Assessment (ERA)
The active substance is a natural substance intended to replace other products on the market, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, melatonin is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

Absorption
The absolute bioavailability of melatonin is reported to be in the order of 15% and varies between 1-56%. Melatonin undergoes extensive first-pass metabolism.

The impact of food intake on melatonin's PK is unclear. Limited literature references with high variability in data are pointing towards an increased exposure under 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.

Bioequivalence study (BC-MEA-21-834)
The Applicant has performed a small relative BA-study in 15 subjects comparing their product with a film-coated tablet, Bio-Melatonin, which is an approved product within the European market. This study was single center, open-label, randomized, fasting, single oral dose of 3 mg, pilot, two-treatment, two-sequence, and two-period crossover study with a washout interval of seven (7) days between dosing. For results see tables below.

Table1. Pharmacokinetic results (baseline corrected)

Parameter	Test Product (Mean ± SD)	Reference Product (Mean ± SD)
C_{max} (pg/ml)	7207.18 ± 3461.28	4158.45 ± 1593.76
AUC_{0-t} (pg.hr/ml)	8069.97 ± 4307.95	7691.09 ± 3609.89
$AUC_{0-\infty}$ (pg.hr/ml)	8117.33 ± 4329.90	7800.00 ± 3689.84
T_{max} (hr)	0.399 ± 0.102	0.809 ± 0.646
$T_{0.5}$ (hr)	0.721 ± 0.187	0.762 ± 0.150
$K_{elimination}$ (hr^{-1})	1.03752 ± 0.34285	0.94582 ± 0.20095

Table 2. Confidence Intervals for the log-transformed Test/Reference Ratios after baseline correction:

Parameter	Point Estimate	Lower Limit	Upper Limit
C_{max}	167.54	140.61	199.62
AUC_{0-t}	102.04	89.23	116.68
$AUC_{0-\infty}$	101.33	88.67	115.81

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. 6-OH-melatonin is the main metabolite which is excreted in the urine as sulphate- or glucuronide conjugate.

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.
Melatonin is mainly eliminated via liver metabolism and an effect of liver impairment is expected. Endogenous melatonin levels are significantly higher in cirrhotic patients compared to controls.

Gender

A nearly 3-fold higher exposure has been seen females compared to male subjects after an oral dose of melatonin in a study with high variability in PK-parameters. No dose adjustments are considered necessary.

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.

The systemic exposure of melatonin increased 4- to 5-fold in subjects using oral contraceptives (Ocs) containing ethinyl-estradiol compared to subjects not using OCs. 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.

Discussion on pharmacokinetics

This is an application according to 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. The Applicant has performed a small relative BA-study in 15 subjects comparing their product with a film-coated tablet, Bio-Melatonin, which is an approved product within the European market. For the primary parameter AUC test and reference were bioequivalent (by standard criteria). However, the other primary parameter Cmax was 1.6-fold higher for the oral solution. By cross-study comparison this is not an extreme Cmax-value. Melatonin is generally considered to belong to the BCS class I substances with high absorption but low bioavailability primarily due to extensive first-pass metabolism. Considering the wide therapeutic window, the clinical pharmacokinetic features of melatonin (high variability), and the need for individual titration of the

dose based on efficacy and tolerability, the difference in Cmax seen in the BA-study is not likely clinically relevant. Overall, an acceptable bridge to the literature data is considered established.

The basic PK-properties of melatonin have been sufficiently well described. While certain references are review articles, which is not considered adequate, these are mostly backed up by original research articles.

Pharmacodynamics
Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin. By binding to melatonin receptors 1 and 2, the downstream signalling cascades have various effects in the body. Physiologically, melatonin secretion increases soon after the onset of darkness, peaks at 2-4 a.m. and diminishes during the second half of the night.

Jet lag, also known as circadian desynchrony, is a sleep disorder in which there is a mismatch with the body's natural circadian rhythm and the external environment as a result of rapid travel across multiple time zones. This common problem affects all age groups but may have more pronounced effects on the elderly, whose recovery rate is more prolonged than that in young adults. A multitude of factors, such as the number of time zones crossed and the direction and timing of flights, play a role in the severity of symptoms experienced. Individual variability accounts for the ability to adapt to a new time zone and the duration of the symptomatic period. Travelers usually experience symptoms after air travel across at least two time zones. Symptoms may include disturbed sleep, daytime fatigue, decreased ability to perform mental and physical tasks, reduced alertness, and headaches.

Clinical efficacy
To evaluate the effect of oral administration of melatonin on jet lag after transatlantic flights crossing several time zones, controlled studies in the Cochrane database and in the databases Medline, Embase, Psychlit and Science Citation Index were reviewed. It was found that melatonin, when taken before sleep time in the destination area, that is between 10 p.m. and 12 p.m., reduces jet lag symptoms. Daily melatonin doses from 0.5 to 5 mg are equally effective. Doses larger than 5 mg do not seem to be more effective. The benefit seems to be greater the more time zones are crossed and smaller for western flights. The timing of melatonin administration seems to be important because if melatonin is taken early during the day, it induces sleepiness, thus delaying adaptation to the local time.

Alcohol should not be taken with melatonin, because it reduces the effectiveness of melatonin.

Melatonin may enhance the sedative properties of benzodiazepines and nonbenzodiazepine hypnotics, such as zaleplon, zolpidem and zopiclone.

Clinical safety
The short-term unfavourable effects of melatonin are generally mild and well established. Reported side-effects of melatonin include:

• abdominal cramps
• alertness decreased
• circadian rhythm disruption
• daytime fatigue
• depression (temporary)
• dizziness
• drowsiness
• unease or dissatisfaction (dysphoria) in depressed patients
• headache
• irritability

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 Melatonin Evolan.

Safety specification

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
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 0.3 signed 28-Jan-2022 is 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 an 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 package leaflet was English.

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

There are no objections to approval of Melatonin Evolan, from a non-clinical point of view, as the non-clinical benefit-risk ratio is considered positive.
From a clinical point of view, well-established use with recognised efficacy and an acceptable level of safety for melatonin for the final narrower indications have been shown. The safety issues that were identified have been adequately addressed in the SmPC and RMP.
The documentation presented covering the drug substance and the drug product is acceptable from a quality point of view.

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

Melatonin Evolan, 1 mg/ml, Oral solution was approved in the national procedure on 2022-07-01.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se