LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Melatonin Apofri
# (melatonin)

# Asp no: 2025-1597

**This module reflects the scientific discussion for the approval of Melatonin Apofri. The procedure was finalised at 2026-05-04. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.**

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# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Melatonin Apofri, 1 mg/ml, Oral solution.

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

# II. EXECUTIVE SUMMARY

## II.1 Rationale for the product

Melatonin is an endogenous hormone synthesised by the pineal gland in a circadian pattern with melatonin levels rising in the evening, reaching maximal values in the middle of the night, and then decreasing to reach minimal values in the morning.

Activity of melatonin at mainly the MT1 and MT2 receptors is believed to contribute to its sleep-promoting properties, as these receptors are involved in the regulation of circadian rhythms and sleep regulation. Because of the role of melatonin in sleep and circadian rhythm regulation, and the age-related decrease in endogenous melatonin production, melatonin may, theoretically, improve sleep quality. Thus, there are several potential indications for melatonin.

The indications of approved melatonin immediate release (IR) formulations in Sweden are limited to short-term treatment of jetlag in adults and treatment of (sleep-onset) insomnia in children and adolescents aged 6 - 17 years with ADHD.

## II.2 About the product

The activity of melatonin at the MT1, MT2 and MT3 receptors is believed to contribute to its sleep promoting properties, as these receptors (mainly MT1 and MT2) are involved in the regulation of circadian rhythms and sleep regulation. Melatonin belongs to the pharmacotherapeutic group: Hypnotics and sedatives, melatonin receptor agonists, and ATC code: N05CH01. EURD for melatonin is: 29/06/2007.

The currently applied product is an oral solution with the strength of 1 mg/ml of the active substance melatonin.

## II.3 General comments on the submitted dossier

The application for Melatonin Apofri, 1 mg/ml, Oral solution, is a Well-established use Art. 10a application submitted according to 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.

## II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The MPA has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the European Community, the MPA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the European Community, the MPA has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
N/A as this is a literature based application.

GLP
As published data from both older and more recent publications are used as references for the non-clinical overview, it is assumed that the majority of studies were not performed in accordance with GLP. This is acceptable in an application under article 10a of Directive 2001/83/EC as amended.

# III. SCIENTIFIC OVERVIEW AND DISCUSSION

## III.1 Quality aspects

**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.

**Drug 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.2 Non-clinical aspects

Pharmacology

Primary pharmacology review of melatonin provided some evidence of promotion of sleep onset and sedative hypnotic activity in study animals. Melatonin is described in the literature as acting at the central nervous system level, modulating the synchronization of the biological clock and promoting sleep through stabilization and phase shifting effects on the suprachiasmatic nucleus of the hypothalamus possibly involving interaction with melatonin MT1 and MT2 receptor subtypes. The beneficial effects of melatonin have been documented in a variety of animal and human models.

In general, the pharmacology of melatonin is well known and well described in publicly available literature. The summaries provided by the applicant are considered sufficient and cause no concerns regarding the safe use of the product of this application.

Pharmacokinetics

Melatonin is rapidly absorbed after oral intake, and the peak plasma concentration is achieved approximately 30-60 min after intake. The mean oral bioavailability varies widely depending on the dose and the animal species. The apparent volume of distribution indicates that melatonin is bound to some parts of the body at higher concentrations than the plasma level of melatonin. Melatonin readily crosses the blood-brain barrier, is promptly distributed in tissues, and rapidly metabolized in the liver mainly by the CYP1A2 enzyme. The bibliographic review of the PK is acceptable.

Toxicology

$LD_{50}$ values are extremely high (grams/kg) by the oral route. In rats, at 24 h after completion of 6 daily injections of melatonin at up to 15 mg/kg histopathology did not reveal any signs of toxicity. In repeated and chronic toxicity studies in laboratory animals, melatonin was found to be a safe compound.

There is limited information in the available literature on the genotoxicity of melatonin. Older, non GLP and non ICH compliant Ames tests show no or low genotoxic or mutagenic potential. No carcinogenicity studies have been performed or found in the public domain but as melatonin is an endogenous substance with no obvious mutagenic potential, the lack of robust cancerogenic studies is acceptable.

There are indications that melatonin affects the reproduction of tested animals (rats, mice and red deer) in several ways, i.e. it may alter the fertility as well as the onset of puberty. As emphasized by the applicant, there are large differences between humans and these animals as seasonal breeders, in particular when it comes to the role of endogenous melatonin in reproduction. In humans, it is

however well 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 a delayed puberty also in humans. These issues are assessed by the clinical assessor and are not further pursued from a non-clinical point of view.

**Environmental Risk Assessment (ERA)**

The applicant has submitted an Environmental risk assessment (ERA). Their assessment concludes that melatonin is a naturally occurring compound, present in several different organisms, and that Phase I assessment as well as screening for PBT stops after Q1. The applicant also mentions that the melatonin of this application is chemically synthesized but indistinguishable from the naturally occurring compound.

The applicant has provided several references as to the levels of melatonin in common foods. It is shown that normal consumption of a variety of foods can easily provide a comparable, or even higher, amount of melatonin than the suggested posology of the product of this application.

As stated in the guidance documents on this topic, there may be exceptional cases where further justification for the absence of studies might be necessary, e.g. when an active substance is classified as being a carcinogen, mutagen, or toxic for reproduction (CMR) or PBT/vPvB.

As stated above, publicly available CMR data are not clear as to melatonin's potential to cause mutagenicity, carcinogenicity or reproductive toxicity. It is however agreed that these potential risks must be put in perspective of the knowledge that melatonin is an endogenous compound, also produced by several other organisms. The consumption patterns of the populations suggested for use of the product of this application should also be taken into account, where the applicant has shown that melatonin is present in several different common foods, and that the daily dose of melatonin could be easily obtained also through the diet.

Despite the divergent information on CMR and the lack of data from specific compartments such as soil, ground water, surface water etc. it is concluded that use of the product of this application in accordance with the suggested SmPC, will not produce any significant increase in the background levels of melatonin.

From a non-clinical point, the application is ready for approval.

## III.3 Clinical aspects

**Pharmacokinetics**
This is an application according to Article 10a well-established use. 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. The basic pharmacokinetic parameters of melatonin are fairly well described by the Applicant. This is considered sufficient for this well-known substance and the Application is approvable from the pharmacokinetic perspective.

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 literature mainly IR tablets have been used, and the relevant comparison would thus be to those. Bridging is based on quality data and accepted in quality section above.

**Pharmacodynamics**
The exact mechanism of action of melatonin is not known, although it seems that MT1 receptors in the suprachiasmatic nucleus (SCN) and MT2 receptors in the retina and the hypothalamus are of importance. Other mechanisms of action, including those that do not involve the MT1 and MT2 receptors, may also be involved (e.g., serotonin receptors in the SCN).

Overall, the clinical overview submitted by the applicant is considered acceptable form a PD perspective.

**Clinical efficacy**
WEU
The Applicant has provided data describing well established use within the Nordic countries, and the material deems sufficient to support well established use of melatonin for the sought indications.

Efficacy

The Applicant has submitted 15 published references to support the efficacy for the indication short-term treatment of jet-lag in adults and 6 published scientific articles to support the indication Sleep onset insomnia in children and adolescents aged 6-17 years with attention deficit hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient.

It is a well composed summary concerning the efficacy and the product information is in line with the dossier. The present WEU application is considered approvable from a clinical efficacy perspective.

**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.

While its short-term use is considered safe and acceptably described in the clinical overview, there are some concerns that long-term use might delay children's sexual maturation, possibly by disrupting the decline in nocturnal melatonin levels that occur at the onset of puberty. The applicant has solved this concern by adding information for guidance the SmPC, which is endorsed.
The present WEU application is considered approvable from a clinical safety perspective.

**Pharmacovigilance system**
The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the MPA considers the Summary acceptable.

**Risk Management Plan**
The Applicant 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 Apofri.

Part II Safety specification
The submitted Risk Management Plan is intended for both Melatonin NET and the duplicate Melatonin Apofri, version 0.2 signed 2025-11-26 contains the following safety concerns:

| Summary of Safety Concerns | |
|---|---|
| Important identified risks | • None |
| Important potential risks | • None |
| Missing information | • None |

Part III Pharmacovigilance Plan

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

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

Part VI Summary of the RMP
The Summary of the RMP has been updated in line with comments raised in previous rounds of assessment and is now endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.2 signed 2025-11-26 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.

**Periodic Safety Update Report (PSUR)**
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

# IV. BENEFIT RISK ASSESSMENT

The applicant Evolan Pharma AB applied for the indications short term treatment of jet lag in adults and insomnia in children and adolescents aged 6-17 years with ADHD, for a 1 mg/ml oral solution.

To support the proposed indications, the applicant has submitted literature data providing satisfactory evidence for efficacy and safety, and the product information reflects the provided dossier.

The quality part of the dossier is acceptable and from a pharmaceutical point of view this application is approvable.

The non-clinical part of the dossier is acceptable and from a non-clinical point of view this application is approvable.

The benefit/risk of this product is positive since the Applicant has responded satisfactorily to the questions raised during the procedure. The procedure is considered approvable.

# V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

## V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N/A

## V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

## V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available on the Swedish MPA website.

## V.4 Package Leaflet (PL)

### V.4.1 Package Leaflet

The approved PL is available on the Swedish MPA website.

### V.4.2 Assessment of User Testing

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 Evolan 1mg/ml oral solution (Dnr: 5.4.1-2020-16504). Assessment of the Bridging proposed by the applicant is attached in Appendix I.

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

# VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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