LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Melatan
(melatonin)

SE/H/2539/01-03/DC

This module reflects the scientific discussion for the approval of Melatan. The procedure was finalised on 2025-01-22. 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 Melatan, 1 mg, 2 mg, 4 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 Melatan, 1 mg, 2 mg, 4 mg, Tablet, is a Well-established use Art. 10a application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and PL as concerned member states (CMS).

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
N/A

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 described in the literature as acting at the central nervous system level, modulating the synchronisation of the biological clock and promoting sleep through stabilisation and phase-shifting effects on the suprachiasmatic nucleus of the hypothalamus possibly involving interaction with melatonin MT1 and MT2 receptor subtypes. In vivo studies in animals examined essentially the sleep induction effects, but the results are difficult to interpret and extrapolate to humans. The beneficial effects of melatonin have been documented in a variety of animal and human models. Besides regulating sleep-wake cycle the hormone has putative contraceptive, antioxidant, anti-aging, and anticancer effects.

Pharmacokinetics
Melatonin is rapidly absorbed after oral intake, and the peak plasma concentration is achieved approximately 30 min after intake. The mean oral bioavailability varies from 17% to 100 % 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 metabolised in the liver mainly by the CYP1A2 enzyme. 6-hydroxymelatonin glucuronide, 6-hydroxymelatonin sulfate, and N-acetyl serotonin are the major metabolites of melatonin.

Toxicology
In acute studies in mice and rats, LD50 values were several grams/kg by the oral route. In repeated and chronic toxicity studies in laboratory animals, melatonin was found to be a safe compound. 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 developmental toxicity study in pregnant Sprague-Dawley rats, the maternal toxicity no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) were 100 and 200 mg/kg/day, respectively, and the developmental toxicity NOAEL was ≥ 200 mg/kg/day. Thus, the developmental toxicity NOAEL was ~1,400-70,000 times the oral doses recommended for sleep induction (0.2-10 mg melatonin). Melatonin is not mutagenic or genotoxic in standard assays such as the Ames test.

Environmental Risk Assessment (ERA)
The active substance is a natural substance, 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.

There are no objections to approval of Melatan from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
No PK studies have been performed using the proposed product. Only published studies using different melatonin strengths and formulations were provided to support the application.

Absorption
The absorption of orally ingested melatonin is complete in adults.

Bioavailability is in the order of 15% (range 9 to 33%) due to extensive first-pass metabolism of melatonin. The T_{max} occurs usually approximately 50 minutes (normal range 15 to 90 minutes) after administration.

Based on limited data with high inter-subject variability, food intake may increase exposure and maximum plasma concentration of melatonin, likely not to a clinically relevant extent.

Distribution
The *in vitro* plasma protein binding of melatonin is approximately 60%.

Biotransformation
Melatonin is mainly eliminated by hydroxylation to 6-hydroxymelatonin in the liver, primarily mediated by CYP1A2 (to a lesser extent by CYP1A1). Quantitatively less important is O-demethylation to N-acetyl-5-hydroxytryptamine mediated by CYP2C19. Melatonin metabolites are mainly eliminated by the urine, ~ 90% as sulphate and glucuronide conjugates of 6-hydroxymelatonin. Less than 1% of the melatonin dose is excreted unchanged in the urine.

Elimination
Metabolites are excreted renally, 80% as 6-sulphatoxy-melatonin.
The elimination half life (t½) is approximately 45 minutes (range 30-60 minutes).
The half-life, on average, is comparable or slightly shorter in children compared to adults.

Special population
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. Cirrhotic patients have been shown to have higher exposure than healthy subjects.

Based on limited data melatonin exposure seems to be higher in females than in males, however variability is high.

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

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 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 increased following caffeine intake. Caffeine is a known CYP1A2 inhibitor. Tobacco smoking was reported to decrease melatonin concentrations.

Discussion on 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. For a WEU application establishing a link between the applied for product and the literature data used to support efficacy and safety is crucial.

Melatonin is generally considered to belong to the BCS Class I drugs such which are highly absorbed and have neither solubility nor permeability limited absorption. The applied for product does not contain any excipients that affect absorption. The Applicant has performed in vitro dissolution comparison with a product used in the literature to support efficacy and safety, and also compared published PK characteristics of different melatonin oral IR formulations. In the presented cross-study

comparison a substantial variability in PK-parameters is seen, also the inter-subject variability within each study is considerable. Melatonin has a wide therapeutic index and the proposed posology is based on titration of the melatonin dose based on the efficacy and safety in the individual patient. Overall, the Applicant has adequately substantiated bridging between their product and the products used in the literature.

The basic pharmacokinetic parameters of melatonin are fairly well-described by the Applicant. The clinical overview has been updated within the procedure and several new supporting references has been provided where this was lacking in the original application. The SmPC has been updated and is now considered acceptable regarding the pharmacokinetic information. The application can be recommended for approval from a pharmacokinetic point of view.

Pharmacodynamics
Melatonin is an endogenously occurring hormone produced by the pineal gland, sometimes designated as the natural sleep hormone of the body. Melatonin is considered to regulate the circadian rhythms and adaptation to the light-dark cycle in the suprachiasmatic nucleus (SCN) of the hypothalamus. Melatonin secretion increases shortly after dark, reaching its peak between 2:00 am and 4:00 am and decreases during the latter half of the night. Melatonin is also associated with a sedative effect and an increased propensity for sleep. Thus, melatonin has both phase-shifting effects (changing the timing of the biological clock), and direct sleep-facilitating effects. Melatonin production declines with age and is lower in middle-aged and elderly patients with insomnia than in good sleepers.

Melatonin belongs to the pharmacotherapeutic group: Hypnotics and sedatives, melatonin receptor agonists, ATC code: N05CH01.

During altered circumstances the problems are related mainly to the fact that melatonin is present at inappropriate time, ie, during the day at higher concentration. When the organism's biological clock is not in phase with its environment which occur for example with jet-lag disorder (JLD) and shift work, the circadian rhythms, sleep-wake cycle, temperature and hormones may desynchronise. Melatonin has both phase-shifting and direct sleep-facilitating effects. The time at which melatonin starts to rise in dim light is called the dim light melatonin onset (DLMO). DLMO serves as the approximate inflection point for advancing and delaying effects of melatonin.

Overall, the clinical PD-summary is considered acceptable.

Clinical efficacy

The following 2 indications are proposed:

{Invented name} is indicated for:
- Short-term treatment of jet lag in adults.
- Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.

<u>Jet lag in adults</u>
Jet-lag is associated with rapid long-haul flights across several time zones. JLD is a disturbance of sleep-wake cycle and occurs when there is a disparity between the external time, i.e., hours of daylight or darkness, and the traveller's endogenous circadian clock (internal time). JLD is usually benign and self- limited, but can occasionally have serious consequences (e.g., an aircraft pilot error).

There is no clear dose-response to melatonin at the individual level. Nevertheless, the applicant provided literature discussing the efficacy of melatonin for the indication jet lag, with a posology of 0.5-5 mg if IR melatonin daily at local time. The applicant's discussion is acceptable for this WEU application.

Insomnia in children and adolescents aged 6-17 year with ADHD
Sleep problems affect about 20-40% of healthy children. This issue is particularly pronounced in children with NDDs and may include 80% of patients. In paediatric practice, 3 groups of disorders that are most often associated with sleep disorders include ADHD, ASD and mood/anxiety disorders. Today IR and PR melatonin medicinal products are authorised for sleep disturbances in children and adolescents with various NDDs including ADHD.

The prevalence and incidence of dispensed melatonin prescriptions, long-term treatment, concomitant dispensation of psychotropic medication, and psychiatric comorbidity, in children and adolescents aged 0–17 years has been studied. The prevalence of dispensed melatonin prescriptions in all age groups increased between 2006 and 2017. In 2017, nearly 80% of all children with dispensed melatonin had concomitant dispensations of psychotropic medications. About 23% of girls and 43% of boys had a concomitant dispensation of another centrally acting sympathomimetic medicine, the majority attributable to medicines for ADHD. Melatonin together with a concomitant medication for ADHD was most common among boys and girls aged 10–12. About half of the children (47% of girls and 50% of boys) had at least one registered diagnosis of mental or behavioural disorders. The most common diagnosis was ADHD across all age groups and genders.

The suggested posology in the SmPC 4.2 is accepted, as it is consistent with other approved melatonin-containing products with the same indication in the EU.

In conclusion, the applicant has provided efficacy data supporting the claimed indications of jet lag in adults and insomnia in children and adolescents with ADHD.

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. To address this concern, specific precautions have been included in section 4.2 of the SmPC, aiming to minimize unnecessary long-term use of melatonin and mitigate associated risks.

The present WEU application is considered approvable from a clinical safety perspective.

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 Melatan.

Part II Safety specification
The MAH has submitted the version 0.2 RMP dated 2024-08-20 and proposed the following summary 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 is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.2 signed 2024-08-20 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

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 PL was Czech.

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 applicant Vitabalans Oy applies for the 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” for Melatan (1 mg, 2 mg, and 4 mg tablets of melatonin).

To support these two indications the Applicant has submitted literature data consisting of published literature references for jet-lag in adults and published literature references for insomnia in children and adolescents with ADHD.

Overall, the submitted efficacy data to support the proposed indication of jet lag in adults and insomnia in children and adolescents with ADHD are considered adequate and deemed sufficient to support WEU.

Safety for short-term unfavourable effects is generally considered mild and well established, since melatonin has been used for decades, including with OTC status, worldwide.

There is no need for conditions under Article 21a/22 of Directive 2001/83EC.

The application is approvable.

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 Melatan, 1 mg, 2 mg, 4 mg, Tablet was positively finalised on 2025-01-22.

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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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