LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Melatonin Italfarmaco
(melatonin)

SE/H/2598/01-06/DC

This module reflects the scientific discussion for the approval of Melatonin Italfarmaco. The procedure was finalised on 204. 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 Italfarmaco, 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 Italfarmaco, 0,5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 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 IT 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
The primary function of melatonin is to regulate circadian biological rhythms, in particular stages of sleep and wakefulness. In diurnal mammals, melatonin is low in the daytime and increasing during night. In addition to the daily circadian rhythmic secretion, there is also a seasonal dependent secretion resulting from changes in duration of daylight at different times of the year. Melatonin generation is strictly photoperiod phase dependent in the pineal gland and in retina.

The amount melatonin produced is controlled by a serial of enzymatic steps starting with the precursor tryptophan followed by the intermediaries 5-hydroxytyptophan, serotonin, N-acetyl serotonin to the final product melatonin. Melatonin acts through the membrane melatonin receptors MT1 and MT2. The most important melatonin receptors involved in sleep regulation are found in the suprachiasmatic nucleus, but melatonin receptors are also found in almost all peripheral tissues.

Successful use of melatonin in a rat animal model of delayed sleep-phase syndrome (DSPS) has been shown. In addition, pinealectomized rats have been shown to respond equally to exogenously administrated melatonin in comparison to controls, i.e. pineal gland secretion of melatonin is not necessary for inducing a normal circadian rhythm. However, it should be mentioned that there are also reports that does not support the importance of melatonin's action on the sleep-phase. A study in baboons, administered orally in doses equally to human dosage (0.5, 3, 5, or 10 mg) either in the early morning hours or late in the afternoon and at all doses and times tested, melatonin did not shift circadian phase.

Pharmacokinetics
Absorption - 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%.

Distribution - Melatonin is highly lipophilic and can readily translocate between blood, cerebrospinal fluid and tissues. The volume of distribution at steady state in rat, dog and monkey ranges between 1.05-1.48 L/kg.

Metabolism - The major metabolism pathway for melatonin is via hydroxylation and to a smaller extent, via acetylation followed by conjugation, primarily with sulphate (70-80%) and to a minor level, with glucuronic acid (5-10%). The liver is the major site of metabolism, primarily by CYP1A subfamily shown in rat, mice, rabbit and human.

Excretion - Studies in rats have shown that approximately 60-70% of intravenously administrated melatonin was found in urine and approximately 15% in the faeces. The major metabolite was sulphate conjugate of 6-hydroxymelatonin and approximately 5-10% was recovered as glucuronic acid conjugate. Sulphate conjugate of 6-hydroxymelatonin is inactive but reflects the endogenous melatonin concentration in plasma.

Toxicology
The results from acute as well as from repeated dose toxicity studies show that melatonin can be toxic at much higher than the therapeutic doses used in humans. Furthermore, long term administration of melatonin in rats or mice did not have negative effects on cardiovascular, endocrine, and reproductive systems.

Melatonin was not mutagenic in in vitro or in vivo tests, indicating that melatonin is not genotoxic

under the conditions of proposed clinical use. Results from experimental studies show that melatonin has no carcinogenic properties.

There is data showing that melatonin affects the levels of male reproductive hormones and the function of spermatozoa; however, these effects are variable and depend on physiological conditions, animal species, etc., making it difficult to draw conclusions about melatonin's effects on the male reproductive system and possible risks of reproductive toxicity. Embryo-foetal development studies in rats and rabbits revealed no direct or indirect harmful effects with respect to pregnancy, foetal survival, foetal body weight or presence of foetal malformations/variations. There is some evidence that exogenous melatonin may alter pubertal timing/onset of puberty in seasonal breeders. The relevancy to humans is however uncertain. However, melatonin short-term use is considered safe and is further described in the clinical part.

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.

IV. CLINICAL ASPECTS

Pharmacokinetics
Absorption
The bioavailability of melatonin is generally in the range of 10-35%, but as low as 3% have been reported. The low bioavailability is largely depending on the extensive first-pass metabolism of melatonin. In one study with high variability about a 2-fold higher exposure of melatonin when administered together with food compared to fasting to condition.

Melatonin appears to have linear kinetics over the range of 0.25 - 10 mg.

Distribution
The proportion of melatonin binds to human plasma protein in vitro have been reported to be 60%. The mean volume of distribution is around 1 L/kg.

Elimination
The mean elimination half-life is reported to vary between 40-70 min. Less than 1% of a melatonin dose is excreted unchanged.
Melatonin is metabolised to its main metabolite 6-hydroxymelatonin, followed by sulfate or glucuronide conjugation. The enzyme responsible for the majority of melatonin metabolism is CYP1A2. To a lesser extent CYP2C19 can demethylate melatonin to N- acetylserotonin.

Special populations
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.

In a single study with high variability a 3-fold higher exposure has been seen females compared to male subjects after an oral dose of melatonin.

The mean peak melatonin serum levels after melatonin treatment tended to be higher and significantly more variable in subjects aged 49-73 years than among the younger subjects aged 20-43 years.

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 *ca* 2-fold higher following caffeine intake. The inhibitory effect was more pronounced in non-smokers compared smokers. Caffeine is a known CYP1A2 inhibitor.

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. The Applicant has provided a sufficient bridging discussion covering both quality and PK aspects which is considered appropriate.

The basic pharmacokinetic parameters of melatonin are fairly well described by the Applicant and supported by adequate references.

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. In addition to MT1 and MT2 receptors additional the mechanism of action described are MT3 (enzyme quinone reductase 2), affinities to calmodulin and nuclear receptors of the retinoic acid receptor family, RORα1, RORα2 and RZRβ, direct inhibition of the mitochondrial permeability transition pore and GABAA receptors. 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).

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 involved in controlling the circadian rhythm and adaptation to the light-dark cycle. Melatonin is also associated with a sedative effect and an increased propensity for sleep.

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

Clinical efficacy
The Applicant applies for the following two indications:

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

Jet lag
Jet lag occurs in travellers who fly across several time zones. Symptoms of jet lag are primarily daytime fatigue and sleep disturbance, but may also include loss of mental efficiency, weakness, and irritability. Jet lag is caused by desynchronization between the body's circadian system and the new day-night cycle at the traveller's destination. The sleep loss caused by the travel itself contributes to jet lag. For instance, after a flight across six or more time zones travellers often need four to six days to adjust to the circadian rhythm in the new time zone. The severity of jet lag symptoms largely depends

on the number of time zones crossed and the direction of travel. Eastbound travel generally causes more disruption due to lost sleeping hours.

Two of the submitted studies can be considered pivotal in supporting the efficacy of melatonin for treating jet lag in adults. Since all concerns regarding the jet lag indication in adults have been adequately addressed by the Applicant, this indication is deemed acceptable from a clinically efficacy standpoint.

Sleep-onset insomnia in children and adolescents aged 6-17 years with ADHD
Several randomized placebo controlled clinical trials, with a total of 338 participants investigating the use of melatonin for insomnia in children and adolescents aged 6-17 year with ADHD, have been retrieved in the public domain. Several RCTs favoured efficacy of melatonin in children with ADHD. Long-terms studies are often both uncontrolled and open-label due to ethical reasons. Brief summaries were provided for some studies, whereas the main study supporting efficacy in children with ADHD included an in-depth discussion of its findings and implications.

The submitted literature data are deemed sufficient to support efficacy of melatonin in short-term treatment of jet lag in adults and sleep-onset insomnia in children and adolescents with ADHD aged 6-17 years, respectively. There are no outstanding issues concerning clinical efficacy. Thus, this 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 sufficiently described in the clinical overview, there were initially some concerns that long-term use of melatonin may delay children's sexual maturation. These concerns were solved by the inclusion of a statement in section 4.2 concerning monitoring at regular intervals to check that the medicine is still the most appropriate treatment. This approach is in line with previous WEU approvals of melatonin and endorsed.

The present WEU application is 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 Melatonin Italfarmaco.

Part II Safety specification
The MAH has submitted the version 1.0 RMP dated 2024-06-14 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

The applicant proposes summary of safety concerns in line with older melatonin containing products, and in accordance with GVP module V, rev 2.

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 1.0 signed 2024-06-14 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 Mellozzan (Dnr 5.4.1-2020-13119) concerning content, and they will use their well-established house style for layout.

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

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

In the present WEU application, the MAH for Melatonin Italfarmaco has applied for the treatment of:
- Short-term treatment of jet lag in adults
- Sleep-onset insomnia in children and adolescents aged 6-17 years with attention deficit hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient.

The dossier and product information have been updated to a satisfactory extent, with no outstanding issues.

The applicant has addressed all questions raised in a satisfactory manner. The RMS has deemed all major issues as resolved since the indication was updated in line with the PSRPH raised by CMS IT.

The applicant has provided satisfactory responses to all questions raised, and the RMS has concluded that all major objections have been resolved.

The benefit-risk assessment of this medicinal product is considered 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 Italfarmaco, 0,5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, Tablet was positively finalised on 2025-08-15.

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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)

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