LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Melatonin Orifarm
melatonin

Asp no: 2019-0568

This module reflects the scientific discussion for the approval of Melatonin Orifarm. The procedure was finalised on 2020-04-22. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Orifarm Generics A/S has applied for a marketing authorisation for Melatonin Orifarm, 1 mg/ml, oral solution. The active substance is melatonin (Melatonin is a hormone produced by the pineal gland during the night in response to light/dark information. The plasma concentration of melatonin exhibits a circadian pattern, rising in the evening with dim light increases progressively to reach maximal values in the middle of the night and then decreases progressively to reach minimal values in the morning).

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

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

III.1 Introduction

Several deficiencies have been identified in the non-clinical part of the dossier. While the non-clinical testing of Melatonin (as submitted) is not up to the current standard, a long clinical experience compensates for the non-clinical shortcomings.

III.2 Pharmacology

Melatonin is synthesized in the pineal gland which is under control by circadian oscillator in suprachiasmatic nuclei of the hypothalamus (SCN). The rhythmic pattern of melatonin secretion is fundamental for time-giving function and adaption of seasonal variations of the environment.

However, a link between in vitro and in vivo studies is still insufficient to demonstrate the effect on the sleeping process and other secondary pharmacological actions. In addition, most pre-clinical studies are performed on nocturnal animals. An extrapolation from pre-clinical studies to the sleeping process in human, should thus be done with caution.

III.3 Pharmacokinetics

Melatonin readily penetrates biological membranes and appears in tissues or body fluids in equal concentrations as in plasma. The terminal half-life is short in rat, dog and Cyno monkey (0.3-0.6 hrs). The oral bioavailability was 53% and 16.9% in rat and dog, respectively (Yeleswaram et al., 1997).

III.4 Toxicology

Single dose toxicity

Melatonin in single dose toxicity studies of mice was most potent around 15-30 minutes after administration followed by a rapid decline in potency. Clinical symptoms were mainly sedative effects and vasodilation. A risk for acute toxicity in animals is low unless excessive doses are applied.

Repeated dose toxicity

In repeated dose toxicity studies, no severe toxicological findings have been reported in the available literature. Melatonin treatment in male rats (4.8 mg melatonin /kg/day for 28-days) have shown mainly effects within the reproductive system such as decreased testes weight and testicular degenerative changes as well as a trend toward a decrease in serum prolactin levels (Prevo, 2000). Decreased testis and increased kidney relative weights were observed in rats administrated with 6 mg/kg/day for 90 days.

Genotoxicity

An Ame's test was supplied by applicant however, insufficiently performed with a reduced number of bacterial strains and is thus not in line with the regulatory guidelines, S2(R1)-ICH. Applicant has provided references from a number of genotoxic studies. Concluded from these studies are that melatonin does not possess any mutagenic nor clastogenic effects.

Carcinogenicity

A number of studies with regard to melatonin's protective role in carcinogenesis has been mentioned, however, all of the studies are performed on either mice spontaneously developing tumours or rats treated with tumorigenic agents prior melatonin treatment. Since there are no controversies between the data on the carcinogenic and anti-carcinogenic potential of melatonin, and since melatonin is indicated only for short term use, no safety issues are expected with regard to carcinogenicity.

Reproductive toxicity

An embryo-foetal toxicity study performed in rat was rather robust in terms of study design and read-outs. No severe maternal or embryofoetal toxicity was reported. The main findings of maternal

melatonin administration on offspring were altered sexual hormone levels or signs thereof; (lower LH, FSH and pro-lactin in males, and lower levels of pro-lactin and LH in females), delayed sexual maturation (female pups), and a shorter gestational period. However, the proposed product is indicated only for short term use and is not indicated for ages younger than 18 years. In addition, the proposed product is not recommended during pregnancy or in women of childbearing potential not using contraception.

III.5 Ecotoxicity/environmental risk assessment

The Applicant has presented a justification for the absence of an environmental risk assessment of the proposed product. The melatonin products applied for are intended to replace the other identical products already on the market and the approval of these products should not result in an increase of the total quantity of melatonin released into the environment.

III.6 Discussion on the non-clinical aspects

A risk for acute toxicity in animals is low unless excessive doses are applied. The most prominent findings after were sedation and vasodilatation. Chronic administration displayed mainly effects within the reproductive system. However, these effects are unlikely to occur since the product is indicated only for short term use by humans >18 years, i.e. in the post-pubertal age. In addition, the proposed product is not recommended during pregnancy or in women of childbearing potential not using contraception.

IV. CLINICAL ASPECTS

IV.1 Introduction

IV.2 Pharmacokinetics

The Applicant has performed one bioavailability study with the proposed product. In addition published studies using different melatonin strengths and formulations were provided to support the application.

Absorption

The performed bioavailability study was an open label, single-treatment, single-period, single dose study in normal, healthy, adult, male human subjects under fasting condition. The subjects received a single oral dose of 3 mL Melatonin Orifarm 1 mg/1 ml solution resulting in a mean plasma C_{max} close to 8800 pg/ml. This is approximately 150 times the nocturnal endogenous C_{max} of melatonin, though both endogenous- and exogenous C_{max} show considerable inter-individual variation.

The absolute bioavailability of melatonin is reported in literature to vary between 1-56%. From a single reference about a 2-fold higher exposure of melatonin was seen when administered together with food compared to fasting to condition, although with high variability in data.

Distribution

The in vitro plasma protein binding of melatonin is about 60.0 %. Melatonin is mainly bound to albumin, alpha1- acid glycoprotein and high-density lipoprotein. The volume of distribution has been reported to be 35 L.

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 metabolized primarily in the liver where it is first hydroxylated in the C6 position by CYP1A2, CYP1A1 and, to a lesser extent, CYP1B1 and thereafter conjugated with sulphate to be excreted as 6-sulfatoxymelatonin; glucuronide conjugation is extremely limited. CYP2C19 and, at lower rates CYP1A2 also demethylate melatonin to N- acetylserotonin.

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. Endogenous melatonin levels are significantly higher in cirrhotic patients compared to controls.

A nearly 3-fold higher exposure has been seen females compared to male subjects after an oral dose of melatonin. However, in the same study a very high inter-individual variability for this parameter was also observed, especially between female subjects.

Systemic exposure of endogenous melatonin decreases with age whether due to decreased release from the pineal gland or increased elimination is unknown.

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 thus the involvement of CYP2C19 in the elimination of melatonin cannot be ruled out.

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.

Conclusion 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 discussed this bridging issue extensively. Melatonin appears to have linear kinetics over the range of 0.25 - 10 mg and is generally considered to belong to the BCS class I substances with high absorption. To support this notion further the Applicant has performed permeability assays employing cultured Caco-2 epithelial cell monolayers showing a high permeability for melatonin. 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.

A small descriptive bioavailability study using the proposed product is included in the application. The results from which were compared to those of other studies retrieved from literature. The studies differ in many aspects making cross-study comparisons uncertain and differences in results difficult to interpret. From the presented cross-study comparison the proposed product appears to be among those IR-formulations that have the shortest T_{max} and highest C_{max}. The potential differences are likely not clinically relevant. Overall a PK-bridge to literature data is considered established.

The basic pharmacokinetic parameters of melatonin are fairly well described by the Applicant. The clinical overview has been updated and new references provided in support of the pharmacokinetic information. The pharmacokinetic properties of this product are sufficiently described to support approval.

IV.3 Pharmacodynamics

Melatonin's role acting on SCN via specific receptors to regulate Circadian rhythms and the sleep-wake timing is well known. The exact mechanism of how exogenous melatonin is acting on conditions involving disruptions in the circadian pattern such as Jet-Lag and Shift Work Disorder is not fully understood.

The application was recommended for approval from a pharmacodynamic point of view.

IV.4 Clinical efficacy

Most published placebo controlled randomised trials presented by the applicant indicate a favourable effect of low doses of melatonin 0.5 -10 mg on jet-lag. The effect appears to be more evident when traveling in an eastward direction compared to westward direction. The most comprehensive meta-analysis also concludes that melatonin is effective in preventing or reducing jet-lag. Eight out of 10 studies in the meta-analysis that fulfilled the inclusion criteria of the analysis found that melatonin, taken close to bedtime at the destination decreased jet-lag from flights crossing five or more time zones.

However, there are several limitations in the available literature. Some studies are briefly described, the source of melatonin unspecified and the blinding not clearly specified. The number of participants in other studies were small and may not be representative of the full target population since they are usually healthy volunteers or certain populations such as cabin-crews.

The outcomes measures vary, and the clinical significance of the outcome measures are not always evaluated. Most studies have used visual analogue scales (VAS) ranging from a subjective assessment by participants of 0 (insignificant symptoms of jetlag) to 100 (very bad symptoms). In some studies, jet-lag symptom or sleep parameters were assessed by a separate VAS and in others a global assessment of jet-lag was used.

In other studies scales assessing cognitive performance such as effect on reaction time and vigilance, and scales measuring effects on mood. There is only a couple of studies [] that have used supportive evidence in terms of neurophysiological investigations such as polysomnograpic evaluations, which is suggested in the EMA guidelines for treatment of Insomnia (EMA/CHMP/16274/2009).

There is also variation in number of time-zone travelled, the dosage and formulation of melatonin used as well as the duration of treatment. There is also a lack of more recent data, most of the studies and meta-analysis are more than 10 years old.
Nevertheless, a biological role of melatonin in regulating the circadian rhythm is well known and there is evidence in literature providing support for the use of short-term use of exogenous melatonin for the treatment of jet-lag in adults for more than 10 years in the EU. Altogether it is considered that efficacy of melatonin in the treatment of jet-lag has been established as the majority of studies in jet-lag subjects showed statistically significant and clinically relevant results.

Timing of intake at bedtime at destination is supported. Individual variations in melatonin metabolism exist, there is no strong basis to recommend exact timing.

The applicant has also provided literature data for the use of melatonin for the treatment of shift work disorder (SWD) even though this indication is not included in the proposed indication. The evidence for use of melatonin for the treatment for SWD is weaker and of lower quality.

There is a lack of solid evidence for WEU for other types of disruptions of the circadian clock than jet-lag in adults such as SWD.

In conclusion, the WEU criteria for efficacy have been fulfilled for the indication “short-term treatment for jet-lag in adults”

IV.5 Clinical safety

Exogenous melatonin seems to be well tolerated during short-term use and at low-doses. Long-term safety data is scarce and needs to be systematically studied. Even though Melatonin Orifarm is indicated for short term treatment it could not be excluded that it is used for longer time frames of for instance cabin-crews.

The most common AEs reported in the published articles included headache, nausea, and sedation. The incidence of AEs is low. There were only a few serious AEs reported.

Melatonin has a well-recognised effect in the regulation of several hormones involved in sexual maturation and reproduction in photoperiodic species such as rodents. The role of melatonin on reproduction in humans is not well established.

Even though the role of endogenous melatonin in regulating the circadian rhythm and the sleep-wake timing is well known, the exact mechanism of how exogenous melatonin is acting on conditions involving disruptions in the circadian pattern such as Jet-Lag and Shift Work Disorder is not fully understood. The applicant was asked to present a summary of relevant secondary pharmacology regarding sexual hormones, metabolic effects related to insulin and regulation of blood glucose levels.

There is a lack of evidence for efficacy and safety of melatonin in children aged 0-18 years with regard to long term endocrine effects on various organ system. The safety and efficacy of Melatonin Orifarm in children aged 0 to 18 years have not yet been established.

Altogether, even though safety data is scarce and safety data in some populations are missing the available evidence from clinical studies and post-marketing sources suggests that tolerability and safety of melatonin, especially when used for a short time period, is acceptable. All issues and questions raised during this procedure from a clinical perspective have been resolved.

IV.6 Risk Management Plans

Risk Management Plan
The MAH has submitted an updated risk management plan (Version 1.2, updated 03.03.2020), 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 Orifarm.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	Off-label use in paediatric patients with sleep disorders
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 1.2 signed 03.03.2020 is considered acceptable, however, the applicant has been asked to re-consider adding off-lable use in paediatric population as an important potential risk.

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.

IV.7 Discussion on the clinical aspects
Altogether it is concluded the B/R balance for the indication short-term jet-lag in adults is positive. It is considered that well-established use in the indication short-term treatment of jet-lag could be demonstrated from a clinical perspective.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Melatonin Pharma Nord 3 mg, film-coated tablets, NL/H/4030/001. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Favourable effects

The physiological role of endogenous melatonin on the regulation of sleep and regulation of the sleep-wake cycle is well known.

There is an extensive literature concerning the use of exogenous melatonin for the treatment of jet-lag and related conditions for a time period extending 10 years in the EU. Most published placebo controlled randomised trials regarding the use of exogenous melatonin presented by the applicant indicate a favourable effect of low doses of melatonin 0.5 -10 mg on jet-lag in adults. The effect appears to be more evident when traveling in an eastward direction compared to westward direction. The most comprehensive meta-analysis () also concludes that melatonin is remarkably effective in preventing or reducing jet-lag. Eight out of 10 studies in the meta-analysis that fulfilled the inclusion criteria of the analysis found that melatonin, taken close to bedtime at the destination decreased jet-lag from flights crossing five or more time zones.

The available evidence from clinical studies and post-marketing experience suggests that exogenous melatonin to be well tolerated during short-term use and at low-doses. The most common AEs reported in the published articles included headache, nausea, and sedation. The incidence of AEs is low and is considered to be appropriately covered in the SmPC.

Several melatonin products are approved for indications associated with jet-lag in other countries in the EU.

Unfavourable effects and uncertainties about favourable effects

Even though the role of endogenous melatonin in regulating the circadian rhythm and the sleep-wake timing is well known. The exact mechanism of how exogenous melatonin is acting on conditions involving disruptions in the circadian pattern such as jet-lag an is not fully understood.

There are several limitations in the available literature presented by the applicant. Most studies are briefly described, the number of participants in each study is small and may not be representative of the full target population since they are usually healthy volunteers or special populations such as cabin-crews.

The outcomes measures vary, and the clinical significance of the outcome measures are not always evaluated. Most studies have used visual analogue scales (VAS) ranging from a subjective assessment by participants of 0 (insignificant symptoms of jet-lag) to 100 (very bad symptoms). In some studies, jet-lag symptom or sleep parameters were assessed by a separate VAS and in others a global assessment of jet-lag was used. In other studies scales assessing cognitive performance such as effect on reaction time and vigilance, and scales measuring effects on mood. There is only couple of studies [] that have used supportive evidence in terms of neurophysiological investigations such as polysomnograpic evaluations. According to EMA guidelines for treatment of Insomnia (EMA/CHMP/16274/2009) two complementary types of trials are required to demonstrate efficacy in the clinical development

programme: (1) trials documenting effects on subjective (usually self-rating) endpoints in the ”natural” setting and (2) trials documenting effects on objective endpoints (polysomnography).

There is also variation in number of time-zone travelled, the dosage and formulation of melatonin used as well as the duration of treatment. There is also a lack of more recent data, most of the studies and meta-analysis are more than 10 years old.

Long-term safety and safety data in special populations is scarce and needs to be systematically studied. Even though Melatonin Orifarm is indicated for short term treatment it could not be excluded that it is used for longer time frames of for instance cabin-crews.

Conclusion

Altogether it is concluded the B/R balance for the indication short-term jet-lag in adults is positive. It is considered that well-established use in the indication short-term treatment of jet-lag was demonstrated.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Description	
Please be informed that the Applicant is requested to provide a risk evaluation concerning the presence of nitrosamine impurities in the product in question and applying the principles outlined in the notice “Information on nitrosamines for marketing authorisation holders (EMA/189634/ 2019)”. If a risk is identified, confirmatory testing should be carried out and batch analysis data submitted. *See Advice_from_CMDh/Nitrosamins*	*The Applicant has confirmed that this will be performed and provided.*

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Melatonin Orifarm, 1mg/ml oral solution, were approved in the national procedure on 2020-04-22.

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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
5.4.3-2020-103878	The application concerns a type II variation to add a second indication, for the treatment of 'insomnia in children and adolescents aged 6-17 years with attention-deficit/hyperactivity disorder (ADHD) where sleep hygiene measures have been inadequate'. The Type II variation application refers to a medicinal product where the active constituent (melatonin) has a well-established medicinal use in the claimed therapeutic indication for at least 10 years, with recognised efficacy and an acceptable level of safety.	Yes	2021-04-19	Approval	The sought indication was supported by public data, no new studies were submitted. Changes were also made to the posology section of the product information, to include dosing regimen for 6-17 years. Also, adverse events related to this age group, and efficacy data were also added.

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

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