LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Melatonin Unimedic Pharma
(melatonin)

SE/H/2029/01/DC

This module reflects the scientific discussion for the approval of Melatonin Unimedic Pharma. The procedure was finalised on 2020-11-11. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Unimedic Pharma AB has applied for a marketing authorisation for Melatonin Unimedic Pharma, oral solution, 1 mg/ml. The active substance is melatonin. Melatonin is involved in the control of the circadian rhythm and the alignment to light/darkness cycle of the environment. Melatonin acts on G-protein coupled receptors in the hypothalamus to regulate sleep-wake rhythms but also neuroendocrine functions and other physiological functions.

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

The application for Melatonin Unimedic 1 mg/ml is submitted as a well-established use application in accordance with Article 10a of Directive 2001/83/EC, as amended.

III.2 Pharmacology

Melatonin is a naturally occurring endogenous hormone produced mainly by the pineal gland in the brain of vertebrates. Melatonin synthesis and secretion is enhanced by darkness and inhibited by light resulting in very low levels during daytime and high levels during night time. The production is circadian and is stimulated by photic stimulus arising after the onset of darkness. The peak of melatonin levels is reached in the middle of the night and decrease to low levels in the second half of the night.

III.3 Pharmacokinetics

The mean oral bioavailability of a dose of 10 mg/kg was 53.5 % in rats and > 100% in dogs as well as in monkeys. As data from lower doses (1 mg/kg) in dogs showed a reduced bioavailability (16.9 %), non-linear pharmacokinetics was indicated in similar way to the human situation, likely depending on first-pass metabolism in the liver.

Melatonin has a relatively rapid distribution among tissues with a serum elimination half-life of 19.8, 18.6, and 34.2 minutes, in rats, dogs, and monkeys, respectively. Steady state distributions volumes in animals range between 1.05 and 1.48 L/Kg. In the circulation melatonin is bound to protein, mostly albumin, but also calmodulin and haemoglobin.

Melatonin is mainly metabolized by CYP1A2. In rat, the main metabolites are inactive and consists of a sulphated conjugate of 6-hydroxymelatonin and a glucuronic conjugated 6-hydroxymelatonin representing about 80 and 10%, respectively, of the exogenous melatonin excreted in the urine.

III.4 Toxicology

Repeat dose toxicity

A study in rats receiving a daily dose of 0 to 5.0 mg/kg in males and up to 7.3 mg/kg in females has been presented in the litterature. The findings in males were a trend toward decrease of serum prolactin concentrations with time at all dose levels of melatonin. Two out of 10 males administered 5 mg/kg bw/day had decreased testes weights and testicular degenerative changes composed of reduced or absent spermatogenesis, spermatidic giant cells and oedema. The reversibility of these changes was not examined. A NOAEL of 0.5 mg/kg/day was established based on changes to male gonads.

Genotoxicity

Melatonin is an endogenously produced molecule, and since the available literature do not point to any mutagenic or genotoxic effect, it is agreed that melatonin does not present any significant genotoxic potential.

Carcinogenicity

Based on the available literature, it is agreed that melatonin is unlikely to induce cancer.

Reproductive and developmental toxicology

Fertility and early embryonic development

The contradictive results regarding effects of melatonin treatment in animals on early embryonic development and sexual hormones affecting sexual maturation and fertility, including male reproductive organs, suggest that the effect may be dependent on at the age of treatment onset. The limited non-clinical information on potential effects of melatonin on male and female fertility can be justified provided that the limited available information is clearly reflected in the SmPC section 4.6, i.e. melatonin should not be recommended in women and men planning pregnancy.

Embryo-foetal development

As regards teratogenicity, developmental toxicity studies have been reported. Rats were dosed by gavage with 50, 100 or 200 mg /kg bw/day (n=25) or with vehicle on gestation day 6 through gestation day 19. Mild maternal toxicity (reduced maternal weight gain) was noted at ≥ 100 mg/kg bw/day. Melatonin had no effect on prenatal survival, foetal body weight, or incidence of foetal

malformations/variations. Based on the findings, a NOAEL for maternal toxicity was set to 100 mg/kg bw/day. The NOAEL for developmental toxicity was 200 mg/kg bw/day (the highest dose tested). No embryo-foetal development studies have been performed on non-rodent species.

Pre-and postnatal development
No data on pre-and postnatal development have been presented.

III.5 Ecotoxicity/environmental risk assessment
A justification for the absence of a complete ERA has been submitted by applicant.

The active substance is a natural occurring substance intended to replace available products, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Melatonin Unimedic oral solution is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects
Since melatonin is a naturally occurring endogenous hormone and has a well-established pharmacologic action and safety profile, there are no concerns to approve Melatonin Unimedic Pharma Oral Solution from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

This well-established use application is based on published literature data only so the applicant has not performed any clinical studies on their own.

IV.2 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. Melatonin is generally considered to belong to the BCS class I substances with high absorption. 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. Endogenous melatonin has been shown to be excreted into human breast milk and therefore it is awaited that this is also the case for administered melatonin.

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 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.

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. 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.

IV.3 Pharmacodynamics

The basic pharmacodynamics of melatonin is described by the applicant. Melatonin is a naturally occurring endogenous hormone produced mainly by the pineal gland in the brain of vertebrates. Melatonin synthesis and secretion is enhanced by darkness and inhibited by light resulting in low levels during daytime and high levels during night-time. The sleep-related effects of melatonin are mediated by membrane G-protein coupled receptors (GPCRs) in the hypothalamus. The exact mechanism of how exogenous melatonin exerts its effect is not completely understood but timing of the administration appears to be important.

Exogenous melatonin may affect the circadian rhythm and could therefore be effective in a number of of sleep related conditions. In addition to its pharmacodynamic effects on regulation of circadian rhythm and sleep, melatonin is suggested to affect a number of different physiological processes, such as thermoregulation, the immune system and different endocrine functions.

Only limited data is presented by the applicant regarding pharmacodynamics related to the proposed indications. This is acceptable considering melatonin well-known roll in regulation of sleep.

IV.4 Clinical efficacy

The two different authorised indications are described separately.

Indication 1: Short-term treatment of jet lag in adults.
The medicinal product is recommended to adult travellers flying across ≥5 time zones, particularly in an easterly direction, and especially if they have experienced jet lag symptoms on previous journeys. Travellers crossing 2-4 time zones can also use it if need be.

The applicant has provided two studies to support the indication.

Study 1
Scientific opinion from the European Commission, European Food Safety Authority (EFSA). The study concludes that alleviation of subjective feelings of jet lag might be of beneficia physiological effect and the melatonin dose should be between 0.5 and 5 mg and should be taken close to bedtime on the first day of travel and on the following few days after arrival at the destination.. The EFSA also concludes that melatonin appears to be safe with short-term use.

Study 2
A review including 10 randomized placebo-controlled trials with melatonin interventions for alleviating jet lag. Selection criteria for inclusion in the review was randomised trials in airline passengers given oral melatonin compared to placebo or other medication. Outcome measures were subjective rating of jet lag or related features such as onset and quality of sleep, day time tiredness, and duration of return to normal. The studies include between 17 to more than 200 subjects each. Melatonin doses used ranged 0.5-8 mg daily.
The review states that eight of ten trials found that melatonin, taken close to the target destination, decreased jet-lag from flights crossing five or more time zones. Daily doses of melatonin 0.5 and 5 mg are similarly effective. The authors conclude melatonin is effective in preventing or reducing jet-lag and that it should be recommended to adult travellers flying across five or more time zones, particularly in easterly direction, and especially if they have experienced jet lag on previous journeys. Travellers crossing 2-4 time zones can also use if need be.

The applicant has provided a description and assessment of the original studies in the review to support the indication as requested. Taken together the data is considered sufficient to support the proposed indication of short term treatment of jet lag in adults.

Indication 2: Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.

The applicant has provided three studies as support for indication.

Study 1
This study is considred the main study supporting the indication and is a randomised placebo controlled study in 107 children 6-12 years old with ADHD and chronic sleep onset insomnia.
The placebo-controlled treatment period was 4 weeks. Enrolled subjects were treated with 3 (<40 kg) or 6 mg (>40 kg) melatonin, or placebo tablets.
Sleep parameters was estimated using actigraphy and sleep logs on seven consecutive days, at baseline, and during the last treatment week. Daytime performance was measured as a rating of each child's core problem, selected based on the reports from the parents and teachers. Several aspects of cognition and quality-of-life were also included in the analysis.
Sleep onset in melatonin-treated subjects was advanced relative placebo by 27 ± 48 minutes and this was accompanied with an increased total time asleep (+19.8±61.9 minutes). These data are supportive of a clinically significant effect in sleep onset in children with ADHD and sleep onset

insomnia. In contrast, parameters describing daytime functioning were overall not significantly impacted by melatonin-treatment.

Study 2
The study was a questionnaire based follow up study to the study to Study 1, with a duration of 3.7 years. The study included responses from 94 of the original 105 children. The long-term efficacy of treatment was evaluated by a questionnaire that "consisted of a combination of multiple choice, numeric, open ended and scaled questions. These questions addressed the following topics: does the child still use melatonin, what is the current dosage, what is the time of administration, what were the reasons for discontinuation melatonin, did the child temporarily discontinue melatonin, what were the effects of discontinuation of melatonin on sleep and behaviour, did the child experience adverse events, did the child experienced unusual co-morbidity during melatonin treatment and what were the effects of melatonin treatment on sleep onset problems, behaviour and mood. In 88% of the participants melatonin was considered to be an effective treatment of sleep onset problems. Self-reported improvement in behaviour and mood was reported in 71% and 61% of the participants respectively. The efficacy data was considered to be supportive natures since it was self-reported.

Study 3
This study investigated the effect of 5 mg melatonin in a small randomised cross-over study in 27 children 6-14 years with ADHD who were treated with stimulants, 19 children were finally evaluated. Each treatment period was 10 days. The primary efficacy endpoint was the mean sleep-onset latency. Sleep onset latency and total night-time sleep was significantly superior to placebo. The initial sleep hygiene measures decreased sleep latency from 91.7 min to 69.3 min on somnolog. After 10 days of treatment, mean sleep latency was 62.1 ±26.6 min on placebo and 46.4±26.4 on melatonin. Two-sample t-tests of the period and crossover differences indicated a significant difference between the sleep latencies for the two treatments. There was no pre-screening with polysomnography, and patients with undiagnosed primary sleep disorders may have enrolled in the study. This study does not tell whether melatonin would have been effective in the absence of sleep hygiene.

IV.5 Clinical safety

The dose margin of melatonin appears favourable and melatonin seems to be well tolerated during short-term use and at low-doses. The number of reported ADRs from literature are subsequently few and not considered severe. The tabulated list of adverse events is also largely in agreement with what is identified for other approved melatonin products.

There are few large long-term placebo-controlled studies systematically studying continuous melatonin therapy over extended periods with sufficient quality standards where safety and adverse events were the primary outcome of the study.

There are currently no limitations for the duration of treatment proposed by the applicant, which implicate that the product could be used for extended time periods. The SmPC clarifies that limited data are available for up to 3 years of treatment. After at least 3 months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. The patient should be monitored at regular intervals (at least every 6 months) to check that Melatonin Unimedic Pharma is still the most appropriate treatment. During ongoing treatment, especially if the treatment effect is uncertain, discontinuation attempts should be done regularly, e.g. once per year.

The applicant has been asked to properly address the long-term safety available in literature and assess the quality of methodologies for collecting safety data in the published material, for instance when it comes to endocrine effects such sexual maturation and growth in children and adolescents. In response to this concern the applicant has clarified that there is no indication that there are major concerns that melatonin delays puberty.

Possible long-term effects of melatonin have been inadequately studied. There are theoretical risks based on biological effects of melatonin, e.g. immunological regulation and endocrinological effects, which could affect puberty development and fertility.

Special warnings and precaution of use

Elderly
Exposure levels to melatonin after oral administration in young and moderately older adults are comparable. It is unclear if significantly older persons are especially sensitive to exogenous melatonin. Caution should therefore be exercised in treatment of this age group and individual dosage is recommended.

Epilepsy
Caution when used in people with epilepsy, as melatonin has been reported to both increase and decrease the frequency of seizures.

Immunological diseases
Occasional case reports have described exacerbation of an autoimmune disease in patients taking melatonin. There are no data regarding use of melatonin in patients with autoimmune diseases. Melatonin are not recommended in patients with autoimmune diseases.

Drowsiness
Melatonin can cause drowsiness. Therefore, the drug should be used with caution if it is likely that the drowsiness may be associated with a safety risk.

Diabetes
Limited data suggest that melatonin taken in close proximity to ingestion of carbohydrate-rich meals may impair blood glucose control for several hours. Melatonin should be taken at least 2 hours before and at least 2 hours after a meal; ideally at least 3 hours after meal by persons with significantly impaired glucose tolerance or diabetes.

IV.6 Risk Management Plans

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 Unimedic Pharma.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	Delay of sexual maturation and development
Missing information	Use in pregnancy and lactation Long-term safety

Pharmacovigilance Plan

Safety concern	**Routine risk minimisation activities**

Delay of sexual maturation and development	Routine risk minimisation activities recommending specific clinical measures to address the risk: Indication in Section 4.2 of SmPC that the patient should be monitored at regular intervals (at least every 6 months) to check that Melatonin Unimedic is still the most appropriate treatment. Inclusion in the package leaflet under section 3: "You or your child should be monitored by your doctor at regular intervals (recommended every 6 months) to check that Melatonin Unimedic is still the right treatment for you/them. "
Use in pregnancy and lactation	Routine risk communication: See SmPC section 4.6

	See PL section 2
Long-term safety	Routine risk communication: See SmPC section 4.4

Risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Delay of sexual maturation and development	Indication in Section 4.2 of SmPC that the patient should be monitored at regular intervals (at least every 6 months) to check that Melatonin Unimedic is still the most appropriate treatment. Inclusion in the package leaflet under section 3: "You or your child should be monitored by your doctor at regular intervals (recommended every 6 months) to check that Melatonin Unimedic is still the right treatment for you/them. "	No additional pharmacovigilance activities.
Use in pregnancy and lactation	Indication in section 4.6 in the SmPC that there is not sufficient data concerning Melatonin Unimedic during pregnancy and lactation.	No additional pharmacovigilance activities.
Long term safety	Indication in section 4.4 of the SmPC that long term effects of melatonin have been inadequately studied.	No additional pharmacovigilance activities.

Summary of the RMP
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.

The submitted Risk Management Plan, version 1.0 signed 23 October 2020 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.

IV.7 Discussion on the clinical aspects

For the first part of the indication the applicant has provided one Scientific opinion from the European Food Safety Authority and summarised the data and conclusions from a review in terms of inclusion criteria, quality, efficacy and safety and clinical significance of the study. The data from the two above listed studies support the proposed indication of short-term treatment of jet lag in adults.
The applicant has provided detailed description and assessment of the studies in the review that support the indication as requested. The short-term unfavourable safety effects of melatonin are considered to be mild and well established.

For the second bullet of the indication, the applicant has provided three studies as support for the proposed indication. One randomised placebo controlled study in children 6-12 years old with ADHD and chronic sleep onset insomnia. A questionnaire based follow up study et al with a duration of 3.7 years, and a small randomised cross-over study in children 6-14 years with ADHD who were treated with stimulants.

Study 1 is considered to be an acceptable study to support the effect of melatonin on insomnia in the studied population. The other studies are is considered supportive for the indication.

Regarding safety, there are few large long-term placebo-controlled studies systematically studying continuous melatonin therapy over extended periods with sufficient quality standards and where safety and adverse events were the primary outcome of the study. Thus, there is a theoretical concern of effects of long-term melatonin treatment. This has been addressed in the SmPC, after at least 3 months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen.

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 AGB, SE/H/2048/001-005. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Melatonin IR products has been extensively used in Sweden, Norway, Denmark and Finland to treat sleep disturbances in children and adults and the use has increased significantly during the last decade or so. However, there is limited detailed data available regarding for which indications melatonin mainly has been used.

The applicant has as requested narrowed the indication for Melatonin Unimedic Pharma. The indication now reads:

- Short-term treatment of jet lag in adults.
  The medicinal product is recommended to adult travellers flying across ≥5 time zones, particularly in an easterly direction, and especially if they have experienced jet lag symptoms on previous journeys. Travellers crossing 2-4 time zones can also use it if need be.

- Insomnia in children and adolescents (6-17 years of age) with ADHD, where sleep hygiene measures are insufficient.

For these two indications sufficient literature data has been provided by the applicant to justify approval.

In conclusion it is considered that well-established use with recognised efficacy and an acceptable level of safety for melatonin for the final indication has been shown. Efficacy for the indication has been demonstrated and the safety issues that were identified are adequately addressed in the SmPC. The quality of the product is considered adequate and the product information is acceptable. Thus, the benefit-risk for Melatonin Unimedic Pharma oral solution, 1 mg/ml i is considered to be positive and the application is recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Melatonin Unimedic Pharma, oral solution, 1 mg/ml, was positively finalised on 2020-11-11.

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)

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