LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Mellozzan
(melatonin)

SE/H/2330/01-06/MR

This module reflects the scientific discussion for the approval of Mellozzan. The procedure was finalised on 2021-02-22. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

EQL Pharma AB has applied for a marketing authorisation for Mellozzan, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, and 5 mg, tablet. 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 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 day-time 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.

III.2 Pharmacology

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-acetylserotonin 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.

III.3 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.

III.4 Toxicology

The studies in the toxicology section are not of adequate quality. These deficiencies are considered acceptable since the clinical safety profile is well-known.

Repeated dose toxicity
A 90- day toxicity study in Long-Evans and Fischer 344 rats was performed in the dose levels 0, 0.005, 0.05, 5.0, 50 or 200 mg melatonin /kg bw/day. Minor adverse events such as dark coloured faeces and reduced body weight gain (≤ 10%) was observed, starting at the dose level of 50 mg/kg.

A life prolongation effect was observed in BALB/c female mice administrated with a daily dose of 10 µg melatonin prior the dark cycle from the age of 15 months. Likewise, a 16-month oral

administration of melatonin to adult CD rats increased the number of rats (87%) surviving up to the age of 27-29 months while only 43% of control rats reached the same age, which was in accordance to the life expectancy.
Severe adverse effects were not reported in the 90 and a 28-day toxicity study. It is agreed that the likelihood for toxicity in human with the proposed dose levels is rather low.

Genotoxicity
Melatonin did not exhibit any mutagenic action in bacterial reverse mutation tests performed with or without metabolic activation.

In vivo mammalian micronucleus test was performed and melatonin was found to reduce LPS- and paraquat-related genotoxicity, likely due to melatonin's antioxidant activity.
Since melatonin is an endogenously synthesised molecule it is unlikely that melatonin possesses a genotoxic potential.

Carcinogenicity
Since melatonin is endogenously produced and not suspected to possess any mutagenic or genotoxic effects, the likelihood for melatonin to exhibit a potential to induce cancer is rather low.

Reproductive and developmental toxicity
Fertility and early embryonic development
Melatonin administration to male hamsters was found to cause testicular regression when administrated within a certain time range. In another study on male rats, melatonin was found to accentuate the effects of injected oestrogen which was found to inhibit spermatogenesis and induce morphological and functional alterations in accessory sexual glands. These events were associated with elevated LH gonadotrophin. These results demonstrated that melatonin in the latter experimental model not only failed to stimulate but provided an additional inhibitory effect on reproductive system in male rat. Another 28-day toxicity study confirmed these results in male rats where melatonin was found to decreased testes weights, induce testicular degenerative changes such as absent spermatogenesis, spermatidic giant cells and oedema. A NOAEL value of 0.50 mg/kg bw/day was established based on testicular changes.

An in vitro study of melatonin did not exert any adverse effects in terms of fertilization and early embryo development in mouse embryos.

Embryo-Foetal development
An embryo-foetal development study in rats, considered to be robust study in terms of design and quality. This NTP study was conducted in agreement with FDA GLP guidelines. Melatonin had no effect on prenatal survival, foetal body weight, or incidences of foetal malformations/variations. A slight maternal toxicity was observed by reduced maternal weight gain at ≥ 100 mg/kg bw/day. Maternal NOAEL and LOAEL was 100 and 200 mg/kg/day, respectively, and the developmental toxicity NOAEL was ≥200 mg/kg/day.

Pre-and post-natal development studies
It is well-known from the literature that melatonin controls the reproductive cycle in many mammals. In addition, it is known that melatonin may exert endocrinological effects which could potentially affect puberty onset and fertility in offspring.

Juvenile toxicity
No juvenile studies have been performed.

III.5 Ecotoxicity/environmental risk assessment

A justification for not submitting an environmental risk assessment has been provided by applicant. This product will not increase the exposure to the environment since it will replace existing similar products on the market.

IV. CLINICAL ASPECTS

IV.1 Introduction

This well-established use application is based on published literature data only. The applicant has not performed any clinical studies of 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. 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.

IV.3 Pharmacodynamics

The basic pharmacodynamics of melatonin was described by the applicant. Melatonin is a naturally occurring endogenous hormone produced mainly by the pineal gland in the brain of vertebrates. Melatonin regulates circadian rhythms, e.g. sleep-wake rhythm, neuroendocrine rhythms and body temperature cycles. Disturbed circadian rhythms are associated with sleep disorders and impaired health. For example, children with multiple developmental, neuro-psychiatric and health difficulties often show melatonin deficiency.

Melatonin acts through different molecular pathways. Several major actions of melatonin are mediated by the membrane receptors MT1 and MT2, which belong to the superfamily of G-protein coupled receptors containing the typical seven trans-membrane domains. The action of melatonin on the melatonin receptors results in two distinct effects: sleep promotion and phase shift of circadian rhythms. Melatonin treatment promotes sleep onset, maintenance, or both, and it induces sleep-like brain waves independent of the time of the day. Melatonin and related analogues phase shift circadian rhythms when given at clock-sensitive times following phase response curves (PRCs) conserved in mammals. Melatonin is also involved in the regulation of the body temperature cycle. The lowering of body temperature induced by melatonin, may contribute to enhanced sleepiness.

IV.4 Clinical efficacy

The two different authorised indications are described separately.

Indication: Short term treatment of jet lag in adults

The applicant has submitted randomized placebo controlled clinical trials found in the public domain, with a total of 1006 participants, investigating the use of melatonin for relieving jet lag.

One main study presented by the applicant was a placebo controlled study including a relatively large sample size (n=320) which also evaluated dose-response. The other studies had generally a smaller sample size, but since they provide a larger amount of data in total they are considered as supportive.

In addition, one review analyses the use of melatonin for the prevention and treatment of jet lag. Also, several of the original clinical studies included in that review were analysed and presented in detail by the applicant. All these studies compared melatonin with placebo, and it was concluded that melatonin is efficient in alleviation of jet lag after flights over five time zones or more and is more pronounced after eastward travel than westward travel.

The studies include between 17 to 320 subject each and the overall study population appears to be relevant and representative of intercontinental flight passengers. Participant age ranged from the mid 20s to mid 60s in most studies.

Melatonin doses used ranged from 0.5-8 mg daily with the large majority of studies using 5 mg melatonin. The effect is seen for the entire dose range studied with some indications of better alleviation at 5 mg as compared to 0.5 mg. Accordingly the proposed posology for Mellozzan is 0.5-5 mg prior to bedtime. If melatonin is administered at a suboptimal time e.g. early in the day, it may cause sleepiness and delay adaptation to local time. 5 days of treatment appears to be sufficient and in order to prevent longer treatment than necessary the maximal duration should be limited to 5 days.

Adverse reactions reported in jet lag studies involving melatonin doses of 0.5 to 8 mg were typically mild, and often difficult to distinguish from symptoms of jet lag. Transient drowsiness/sedation, headache and dizziness/disorientation were reported.

In conclusion, sufficient support for the proposed indication of short-term treatment of jet lag in adults has been submitted.

Indication: Insomnia in children and adolescents aged 6-17 years with ADHD when sleep hygienic efforts have not been sufficient

The applicant presented randomized placebo controlled clinical trials found in the public domain, investigating the use of melatonin for insomnia in children and adolescents aged 6-17 years when sleep hygienic efforts have not been sufficient.

Two trials specifically studied children with an ADHD diagnosis, where the main study included children with ADHD and suffering from sleep onset insomnia.

The doses of melatonin were weight-based with 3 mg for children <40 kg and 6 mg for those above 40 kg. The timing of dosing was 7 PM for all, which is appropriate according to the theories of the chronobiotic effects of melatonin. However, the dosage regimen was in the dose range for a hypnotic effect of melatonin to occur as well.

Daytime performance was measured as a rating of each child's core problem, selected based on the reports from the parents and teachers. In addition, several aspects of cognition and quality of life (QoL) were measured.

Melatonin treatment led to a statistically significant advance of dim-light melatonin onset by 44.4 ± 67.9 minutes whereas placebo resulted in a slight delay of 12.8 ± 60.0 minutes. This difference reflects the phase-shifting chronobiotic effects of melatonin. Sleep onset was also advanced by 26.9 ± 47.8 minutes with melatonin, and slightly delayed by placebo (10.5 ± 37.4 minutes). Sleep latency was shortened from 53.0 ± 22.0 min at baseline by 21.3 ±33.0 min by melatonin, and slightly lengthened from 47.3 ± 23.2 min at baseline by placebo (+3.0 ±31.7 min). A shortened sleep latency is often considered clinically relevant, if the mean treatment difference from baseline is in the range of 20-30 min. The total sleep time (baseline 519 min) was slightly increased by melatonin by around 20 min.

The endpoints related to daytime functioning were overall not significantly affected by melatonin treatment. The most frequently reported core problems, as reported by the parents, were "easy to anger" (36.0%), "sleep-onset problems" (31.8%), and "attention problems" (23.3%). The core problem according to the parents were statistically significantly improved by melatonin, but this difference lost statistical significance when one of the major core problems (sleep-onset problems) was removed from the analysis. In addition, differences in changes of teacher-reported core problems were not significant.

The overall impression from the main clinical study was that it was well-designed, of border-line size, and of short duration. The results demonstrate a pharmacodynamic chronobiotic effect of melatonin on dim light melatonin onset (DLMO) and a clinically relevant effect on sleep latency. However, these effects on sleep don't translate into clinically relevant effects on daytime function.

The favorable effect of melatonin on insomnia in children and adolescent aged 6-17 years with ADHD was demonstrated for short-term use, and in a follow-up study for up to 3 years use. A third, smaller sized study, was considered supportive for the indication. In conclusion, sufficient support for the proposed indication "Insomnia in children and adolescents aged 6-17 years with ADHD when sleep hygienic efforts have not been sufficient" has been submitted.

In line with the posology recommended for previously approved melatonin products, the applicant suggests a dosing titrated based on efficacy where the minimum efficacious dose is titrated to achieve the desired effect on alleviating the advance sleep onset with acceptable adverse events. One study, even if not performed specifically in children with ADHD, showed that doses as low as 0.5 mg can be effective in inducing sleep. In the proposed SmPC it is stated that a starting dose should by between 0.5 to 2.0 mg and a maximum dose is 5 mg, which is acceptable.

IV.5 Clinical safety

It is agreed that the dose margin of melatonin appears favourable and melatonin seems to be well tolerated during short-term use and at low doses and the number of reported ADRs from literature are subsequently few and not considered severe. However, data for long-term safety and safety in special populations for melatonin are not extensive.

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 Mellozzan 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 Mellozzan 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 are no major concerns that melatonin delays puberty. However, there is a theoretical concern of effects of long-term melatonin treatment on sexual maturation and growth. Long-term safety in children and adolescents and effects on sexual maturation and development in children and adolescents are issues that have been included in the risk management plan as important potential risks.

IV.6 Risk Management Plans

The MAH has submitted a revised 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 Mellozzan.

RMP Version number: 0.3

Data lock point for this RMP: 04-Jul-2019
Date of final sign-off: 30-Dec-2020

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	Long-term safety in children and adolescents. Effects on sexual maturation and development in children and adolescents
Missing information	Use in pregnancy and lactation Long-term safety

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

The submitted Risk Management Plan, version 0.3, signed Dec 30, 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 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.

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, a detailed independent analysis of the individual referred clinical studies has been performed by the applicant, showing that melatonin, taken close to bedtime at the destination decreased jet lag from flights crossing five or more time zones. The data from the submitted studies support the proposed indication of jet lag in adults.

For the second part of the indication, one randomised placebo-controlled study in children 6-12 years old with ADHD and chronic sleep onset insomnia is considered to be an acceptable study to support

the effect of melatonin in chronic sleep onset insomnia. The other referred studies are 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 on sexual maturation and growth. This has been addressed in the SmPC and the risk management plan.

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 PIL was Swedish.
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 final accepted indications for Mellozzan are:

- Short term treatment of jet lag in adults
- Insomnia in children and adolescents aged 6-17 years with ADHD when sleep hygienic efforts have not been sufficient.

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 indications have been shown. Efficacy for the indications have been demonstrated and the safety issues that were identified have been adequately addressed. The application is recommended for approval from a quality perspective and the product information is considered acceptable. In summary, the benefit-risk for Mellozzan, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, and 5 mg, tablet is considered 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

Mellozzan, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, tablet, was approved in the national procedure on 2021-02-22.

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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
SE/H/2330/01-06/MR	Initial Mutual Recognition Procedure	Yes	2023-04-26	Approval	N/A

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

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