LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Melatonin EQL Pharma
(melatonin)

This module reflects the scientific discussion for the approval of Melatonin EQL Pharma. The procedure was finalised on 2023-04-25. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Melatonin EQL Pharma, 1 mg/ml, oral solution.

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 EQL Pharma, 1 mg/ml, oral solution, is an application submitted according to Article 10a of Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

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
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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 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.

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 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
Single dose toxicity
Melatonin, as a natural occurring hormone, possess low toxicity risk. Among the reported symptoms in single-dose studies were sedation, lethargy and vasodilatation demonstrated as redness of ears and limbs and decrease muscle tension, restriction of motor activity, ataxia. Symptoms such as tendon reflexes, decreased body temperature and respiratory depression was observed preceding death.

The reported symptoms were observed at very high dose levels with an exposure in large excess of what can be achieved in human with the proposed clinical dosage. This is considered acceptable.

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. One female Long-Evan rat had dilated uterus. Mean retinal outer nuclear layer thickness was studied in a 28-day toxicity study in the same rat models and dose levels and was performed in three different light periods. No adverse findings were reported in either sex or treatment group. A NOAEL value of 200 mg/kg bw/day were established.

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 28-day toxicity studies. In addition, considering the high dose levels in these studies, 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. Contrary, melatonin was found to have protective effects against 7,12dimethylbenz[a]anthracene induced lesions tested in Salmonella TA100 and TA102 as well as a slight dose-related protective effect against clastogenicity tested in a CHOK1 cell comet assay.

In vivo mammalian micronucleus test was performed in LPS-treated rats and paraquat-induced mice. Melatonin was found to reduce LPS- and paraquat-related genotoxicity. This effect is, suggested by authors, likely due to melatonin's antioxidant activity.

Since melatonin is an endogenously synthesised molecule and no mutagenic or genotoxic effects have been proposed in the available literature, it is agreed that melatonin is unlikely to have a genotoxic potential.

Results following chronic melatonin consumption on genotoxic and mutagenic parameters in old Swiss mice demonstrated that melatonin prolonged the life span of the animals. Melatonin was effective in reducing DNA damage caused by ageing, presenting antigenotoxic and antimutagenic activities, independently of initiation age.

Carcinogenicity

It is currently not possible to conclude the carcinogenic potential of melatonin in the provided non-clinical dossier. 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 estrogen 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.

Human studies, however, have shown that low dose long-term melatonin administration had no effect on reproductive hormones in normal humans, which indicate that the risk for adverse effects on male fertility is low in humans.

Melatonin has an intra-follicular role in the ovary. It is secreted by the pineal gland and has been reported to be taken up into the follicular fluid from the blood. The free radicals produced within the follicles, especially during the ovulation process, are scavenged by melatonin, and reduced oxidative stress may be involved in oocyte maturation and embryo development. Evidence is pointing to the fact that melatonin treatment for infertility in women increases intra-follicular melatonin concentrations which subsequently reduces intra-follicular oxidative damage and elevates fertilization and pregnancy rates. Exogenous melatonin treatment has even been suggested as a possible new cure for improving not only oocyte quality but also sperm quality in infertile patients.
Immature female rats were injected with 1–20 μg of melatonin daily for 28 days, there was a highly significant decrease in ovarian weight and a delay in spontaneous vaginal opening and onset of estrus. Melatonin (in the μg-range) for 28 days caused a significant decrease in the weight of the ovary, delay in spontaneous vaginal opening and onset of oestrus in immature female rats. Similar results were obtained in hamsters, showing that 20 μg /kg melatonin reduced the number of ovulating adult females. On the contrary, in humans there are indication that melatonin, through its antioxidative properties, can have a beneficial effect on female intra-follicular oxidative damage and elevates fertilization and pregnancy rates.

Embryo-Foetal development
In a robust embryo-foetal development study in rats, 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 and fertility in offspring. However, animal studies have also shown that melatonin has no obvious detrimental effects on mouse and rat embryo development both in vitro and in vivo.

Juvenile toxicity
There is some evidence that exogenous melatonin may alter pubertal timing in seasonal breeders. From these animal model for the onset of puberty. The relevancy to humans is however uncertain. One of the longitudinal studies in humans suggested that long-term melatonin use might be linked to a delay in puberty onset.

Environmental Risk Assessment (ERA)
A justification for not submitting an environmental risk assessment has been provided by applicant. It is agreed that this product will not increase the exposure to the environment since it will replace existing products on the market.

IV. CLINICAL ASPECTS

Pharmacokinetics
No clinical PK studies have been performed using the proposed melatonin oral solution product. Only published studies/articles using different melatonin strengths and formulations were provided by the Applicant to support the present application.

Absorption
The bioavailability of melatonin is generally variable and in the range of 10-35%. The relatively low bioavailability is largely related to the extensive first-pass metabolism of melatonin.

In one clinical study with high variability and limited number of study subjects (i.e., 4-5 study subjects per drug formulation) about a 2-fold higher exposure of melatonin was observed when administered together with food compared to fasting conditions. However, these data are considered too limited to describe the exact magnitude of food impact on PK parameters of melatonin and its potential clinical relevance.

Distribution
Plasma protein binding *in vitro* is about 60% (fu = 40%). Volume of distribution during the terminal elimination phase is reported about 1 L/kg.

Elimination
The mean elimination half-life is reported to vary between 30 - 60 min. Less than 1% of a melatonin dose is excreted unchanged in urine.

Melatonin is metabolised primarily via CYP1A2 enzyme, with some contributions from CYP1A1 and CYP2C19 enzymes.

Special populations
Decreased renal function is not expected to influence the elimination of melatonin since <1% of the dose is excreted unchanged in the urine following an oral dose.

Melatonin is mainly eliminated *via* liver metabolism, and therefore an impact of liver impairment on the melatonin PK is expected. Cirrhotic patients have been shown to have higher exposure than healthy subjects.

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

Interactions
A 17-fold higher total exposure of melatonin was seen when co-administered with fluvoxamine compared when administered alone. Fluvoxamine is a known strong inhibitor of both CYP1A2 and CYP2C19.

Other CYP1A2 inhibitors also increase melatonin exposures e.g., 5-or 8-methoxypsoralen, cimetidine, oestrogens and caffeine.

CYP1A2 inducers such as carbamazepine and cigarette smoking may decrease melatonin levels.

Discussion on pharmacokinetics

This is an application according to Article 10a well-established use (WEU), which is primarily based on bibliographic data on melatonin. 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 product in question and the literature data used to support efficacy and safety is considered crucial.

The Applicant has not provided BE-study with the present melatonin product. However, since melatonin can be generally considered as a substance belonging to the I class of BCS, and since provided literature data are considered sufficient for the present application, it is agreed that clinical data generated with simple IR formulations of melatonin can be considered applicable to the current oral solution product. Therefore, no comparative clinical PK study is requested in this particular case.

Finally, all the basic pharmacokinetic parameters of melatonin are generally well described and

supported by the Applicant with adequate literature data.

Pharmacodynamics
The national WEU application for Melatonin EQL Pharma, oral solution (1 mg/mL) is supported by a Clinical Overview which is almost identical to the previously submitted document for Melatonin EQL Pharma immediate release tablets, by the same applicant. Therefore, no detailed re-assessment of this document is performed for the purpose of the present application. The bibliographic data supporting the clinical pharmacodynamics, efficacy and safety of melatonin in the sought indications are summarised below.

Melatonin is synthesised in multiple sites throughout the body including the pineal gland, non-endocrine organs and tissues, including the retina, harderian glands (accessory to the lacrimal glands), bone marrow, skin, serotonin-producing cells in the gastrointestinal tract, cerebellum, and immune system. Pineal cells first convert tryptophan in the blood into serotonin through hydroxylation and decarboxylation. N-acetyltransferase transforms serotonin into N-acetylserotonin, which is subsequently methylated by hydroxylindole-O-methyltransferase to form melatonin. Pineal melatonin concentrations do not exceed 1 µmol/L, whereas concentrations of melatonin secreted by other tissues and organs range from 0.7 to 30 µmol/L. Melatonin levels change throughout life. In humans, melatonin production start at 3-4 months of age. Levels increase progressively during childhood, peaking between the ages of 8 and 10 years. Melatonin synthesis decreases dramatically during puberty. After the age of 40-45 years, melatonin levels decrease progressively, and by the age of 70 they represent barely 10% of prepubertal levels.2 In healthy individuals, melatonin is synthesised in response to darkness, between 20:00 and 22:00, peaking between 00:00 and 03:00, regardless of the sleep stage. After that, melatonin synthesis progressively decreases, remaining very low during the day. Melatonin levels peak when body temperature is lowest. At night, peak plasma melatonin levels range from 100 to 200 pg/mL; concentrations range from 10 to 30 pg/mL during the day. Daylight exposure is the main factor in the regulation of melatonin secretion.

Effects on sleep and circadian rhythm
Actions 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 induces sleep-like brain waves independent of time of 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 considered to be involved in the regulation of the body temperature cycle. The lowering of body temperature induced by melatonin, may contribute to enhancing sleepiness.

Clinical efficacy

The following two indications are included in section 4.1 of the SmPC document:

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

The proposed indications are accepted.

Jet lag in adults
The applicant has submitted nine 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.

As a main study the applicant presents from 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 evidence by the applicant.
Eight of the studies plus two additional studies were included in a Cochrane systematic review and a meta-analysis.

This review analyses the use of melatonin for the prevention and treatment of jet lag. Also, eight of the original clinical studies included in that review were in detail analysed and presented in the applicant's response. All these studies compared melatonin with placebo; In addition, one compared melatonin with a hypnotic, zolpidem.

Of the eight high quality studies, six favoured melatonin while two studies) favoured neither melatonin nor control. One study did not favor neither melatonin nor control despite a large sample size (n=339) which may be because of a design fault. The studies included 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 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 Melatonin EQL Pharma is 0,5-5 mg prior to bedtime.

Detailed review of the eight studies included in the Cochrane review supports and strengthens the conclusions 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.

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.

Insomnia in children and adolescents aged 6-17 year with ADHD
The applicant presents 4 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 ADHD diagnosis and included 105 respective 33 participants.

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.

The EMA insomnia guidelines state that efficacy should be demonstrated not only on sleep parameters but also on daytime performance. 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). This is however of very doubtful clinical relevance. 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 this 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 smaller sized study was considered supportive for the indication. Overall, these studies support efficacy for the proposed indication to use IR melatonin in “Insomnia in children and adolescents aged 6-17 years with ADHD when sleep hygienic efforts have not been sufficient”.

All studies supporting the jet lag indication as well as the indication of insomnia in children and adolescents aged 6-17 year with ADHD were conducted with IR formulations of melatonin. Thus, extrapolation of efficacy results obtained with PR formulations of melatonin is not relevant for this application.

In line with the posology recommended for previously approved IR 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. Some published data, albeit not performed 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.

Overall conclusions on clinical efficacy

The literature data submitted including the Cochrane review is sufficient to support the proposed indications of short-term treatment of jet lag in adults and insomnia in children and adolescents aged 6-17 year with ADHD. The SmPC is acceptable.

Clinical safety

Adverse events were reported in most of the published randomized clinical trial evaluating melatonin for the prevention and treatment of jet lag. Most adverse events or symptoms included hypnotic effects, headache or ’heavy head’, disorientation, nausea, and gastrointestinal problems. All the adverse events reported in the trials occurred during treatment and appear to have been of short duration.

Paediatric melatonin safety/tolerability trials are limited but there is no evidence that short-term melatonin use has serious adverse events. Recent studies suggest that paediatric PR melatonin is safe and effective for long-term treatment in children and adolescents. The most frequent adverse reactions reported were fatigue, often reported after dose escalation and quickly resolved by decreasing the dose, sleepiness and mood swings. There were no observed detrimental effects on children's growth and pubertal development and no withdrawal or safety issues related to the use or discontinuation of the drug. Discontinuation of medication was not associated with withdrawal effects nor rebound insomnia.

While its short-term use is considered safe, there are some concerns that long-term use might delay children's sexual maturation, possibly by disrupting the decline in nocturnal melatonin levels that occur at the onset of puberty. There are only few studies that have examined pubertal timing in children and youth given melatonin on a long-term basis. Thus far studies have not found untoward effects on sexual maturation. Further experimental studies on the impact of melatonin on puberty, notably in non-seasonal mammals, and advances in the research about the intermediary processes between melatonin and kisspeptin activation, could ultimately inform us about the potential influence of exogenous melatonin on puberty.

Melatonin does not have drug abuse potential. Exogenous melatonin has not been reported to exert tolerance and does not cause dependence or a withdrawal effect in general.

In summary, the most commonly reported AEs for melatonin were related to headache, gastrointestinal disorders, fatigue, drowsiness, mood or psychomotor or neurocognitive functions. Most AEs were considered mild and of limited duration. However, data on long-term safety and safety in special populations for melatonin are scarce in the public literature.

Overall conclusions on 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.

Concerning the indication insomnia in children and adolescents with ADHD, there is currently no limitations for the duration of treatment proposed by the applicant, which implicate that Melatonin EQL Pharma oral solution could be used for extended time periods. The provided 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 EQL 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. This is accepted.

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 has been included in the RMP as important potential risks (see below).

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 EQL Pharma.

Safety specification

Proposed list of safety concerns

Table SVIII.1: Summary of safety concerns

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	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 revised Risk Management Plan, version 0.2 signed 02 November 2022, is considered acceptable.

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 EQL Pharma.

Safety specification

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 0.2, signed 02 November 2022, 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.

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 Melatonin AGB (SE/H/2048/01-05/MR) concerning content and they use their common house style for layout.

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

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The applicant has applied for Melatonin EQL Pharma (melatonin oral solution 1 mg/ml) in the treatment of:

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

Given that well-established use with recognised efficacy and an acceptable level of safety for melatonin for the sought indications has been sufficiently demonstrated, these indications are accepted. There are no outstanding issues regarding non-clinical and clinical aspects. Thus, there are no objections to approval of Melatonin EQL Pharma from a non-clinical and clinical point of view

The quality of Melatonin EQL Pharma is acceptable. The excipients are well-known and commonly used in similar products. The choice of preservatives is justified as well as the amounts used. The levels are acceptable also from a paediatric perspective. From a quality point of view this application is recommended for approval. The product information is acceptable.

The benefit/risk is considered positive, and the application is therefore recommended for approval.

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

Melatonin EQL Pharma, 1 mg/ml, oral solution was approved in the national procedure on 2023-04-25.

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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