SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Melatonin EQL Pharma 1 mg/ml oral solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml oral solution contains 1 mg melatonin.

Excipient with known effect
1 ml of solution contains 1 mg methyl parahydroxybenzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Clear, colourless to slightly yellowish solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

{Invented name} is indicated for:

- Short-term treatment of jet lag in adults.
- Insomnia in children and adolescents 6 - 17 years with ADHD, where sleep hygiene measures have been insufficient.

4.2 Posology and method of administration

Dosage

Adults with jet lag
The recommended dose is 0.5 - 5 mg melatonin (0.5 - 5 ml {Invented name}) daily for a maximum of 5 days. Recommended starting dose: {Invented name} 2 ml (equivalent to 2 mg melatonin).

The dose should be taken at the time of bedtime at the destination when travelling across 5 time zones or longer, especially when travelling east. If necessary, it can also be used by travelers crossing 2 - 4 time zones.

As taking melatonin at the wrong time may result in a lack of effect or cause a side effect following jet lag recovery, {Invented name} oral solution should not be taken before 20:00 or after 04:00 at destination time.

As alcohol may impair sleep and potentially exacerbate some symptoms of jet lag (e.g. headache, morning fatigue, ability to concentrate), it is recommended not to consume alcohol concomitantly with {Invented name} (see section 4.5).

Maximum treatment is 16 times a year.

Insomnia in children and adolescents with ADHD
Treatment should be initiated by a physician experienced in ADHD and/or treatment of sleep disorders in children.

The recommended starting dose of {Invented name} oral solution: 0.5 - 2 ml (equivalent to 0.5 - 2 mg melatonin) 30 - 60 minutes before bedtime.

The dose of melatonin may be increased by 1 ml {Invented name} (equivalent to 1 mg melatonin) per week until effect is achieved, up to a maximum of 5 mg melatonin (5 ml {Invented name}) per day, regardless of age. The lowest effective dose should be sought.

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 discontinuing treatment if no clinically relevant treatment effect is seen. The patient should be monitored regularly (at least every 6 months) to ensure that {Invented name} remains the most appropriate treatment. During treatment, especially if the efficacy of treatment is uncertain, withdrawal attempts should be made regularly, for example once a year.

If the sleep disorder has occurred during treatment with ADHD medicinal products, dose adjustment or switching to another product should be considered.

Special populations

Elder
As the pharmacokinetics of melatonin (immediate-release) are generally comparable in young adults and elderly people, no specific dosing recommendations for elderly persons are provided.

Renal impairment
The effect of any degree of renal impairment on the pharmacokinetics of melatonin has not been studied. Caution should therefore be exercised when administering melatonin to patients with renal impairment (see section 5.2).

Hepatic impairment
Limited data show that the plasma clearance of melatonin is significantly reduced in patients with cirrhosis of the liver. {Invented name} is not recommended in patients with moderate or severe hepatic impairment (see section 5.2).

Paediatric population

Children under 6 years
{Invented name} is not recommended for children under 6 years of age with ADHD.

Method of administration
Oral use.
A dosing syringe is included in the carton of the medicine. The size of the syringe is 5 ml with a scale graduation of 0.1 ml.

Instructions for use:
1. Remove the bottle cap.
2. Put the syringe in the bottle. Measure the dose by slowly pulling out the plunger to the correct volume. Read the dose towards the top edge of the plunger.
3. The child should sit upright. Aim the tip of the syringe at the inside of the cheek. Slowly push in the plunger and allow the child to swallow naturally. Too fast administration of the medicine may cause discomfort.
4. Clean the inside of the syringe after each use.

Food may increase melatonin plasma concentrations (see section 5.2). Intake of melatonin and carbohydrate-rich meals may impair blood glucose control for several hours (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Possible long-term effects of melatonin have been inadequately studied. There are theoretical risks based on biological effects of melatonin, such as immunological regulation, effects on the threshold of epileptic seizures and endocrinological effects, which could affect pubertal development and fertility, respectively.

Drowsiness
Melatonin can cause drowsiness. Melatonin should therefore be used with caution if the effects of drowsiness are likely to pose safety risks.

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

Epilepsy
Caution should be used when used in people with epilepsy, as melatonin has been reported to both increase and decrease seizure frequency.

Diabetes
Limited data suggest that melatonin taken in close proximity to 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, preferably at least 3 hours after a meal in people with significantly impaired glucose tolerance or diabetes.

{Invented name} contains methylparaben
This medicinal product contains methylparaben (methyl parahydroxybenzoate) which may cause allergic reactions (possibly delayed).

4.5 Interactions with other medicinal products and other forms of interaction

Pharmacokinetic interactions
Melatonin is mainly metabolized via CYP1A enzymes. Interactions between melatonin and other active substances that affect CYP1A enzymes are therefore possible.

CYP1A2 inhibitors
CYP1A2 inhibitors can significantly increase the plasma concentration of melatonin. Concomitant treatment with melatonin and the CYP1A2 inhibitor fluvoxamine (including CYP2C19 inhibitors) should be avoided. A clinical study showed that treatment with fluvoxamine and melatonin simultaneously produced a 17-fold higher AUC and a 12-fold higher C_{max} for melatonin compared to administration of melatonin alone. Caution should be used when melatonin is used concomitantly with the following CYP1A2 inhibitors: ciprofloxacin, norfloxacin and verapamil.

Combined hormonal contraceptive: Contraceptives containing ethinylestradiol and progestogen may inhibit CYP1A2 and may lead to 4 - 5 times higher melatonin concentration. The dose of melatonin may need to be lowered.

Hormonal replacement therapy: In postmenopausal women, hormone replacement therapy has been reported to delay the T_{max} of melatonin without other effects on melatonin concentration or melatonin rhythm.

Through interaction with moderately pronounced inhibitors of CYP1A2, an increase in the plasma concentration of melatonin is expected. Therefore, caution should be exercised in patients taking 5- or 8-methoxypsoralen (5- or 8-MOP), cimetidine or caffeine.

CYP1A2 inducers
CYP1A2 inducers may reduce plasma concentrations of melatonin.
Dose adjustment of melatonin may be needed if given concomitantly with the following CYP1A2 inducers: carbamazepine, phenytoin, rifampicin, omeprazole and cigarette smoking (halved exposure compared to after 7 days of abstinence from smoking).

Pharmacodynamic interactions
Adrenergic agonists/antagonists, opiate agonists/antagonists, antidepressants, prostaglandin inhibitors, tryptophan and alcohol affect the endogenous secretion of melatonin in the epiphysis. It is not known whether these interactions have clinical significance.

Alcohol
Alcohol should not be taken together with melatonin as it may reduce the effect of melatonin on sleep.

Nifedipine
Melatonin may reduce the hypotensive effect of nifedipine. Caution must be exercised during concomitant use of melatonin and dose adjustment of nifedipine may be required. Since it is not known whether this is a class effect, caution should be exercised when combining melatonin with other calcium channel blockers.

Warfarin
Case reports have reported that patients treated with melatonin and vitamin K antagonists such as warfarin may cause either increased or decreased prothrombin levels and one study has shown decreased levels of factor VIII:C and fibrinogen. The combination of warfarin and other vitamin K antagonists with melatonin may require dose adjustment of the anticoagulants and should be avoided.

Benzodiazepine-related hypnotics
Melatonin may enhance the sedating properties of benzodiazepine-like hypnotics, e.g. zolpidem. Concomitant treatment with melatonin should be avoided.

NSAIDs
Prostaglandin synthesis inhibitors (NSAIDs) such as acetylsalicylic acid and ibuprofen taken in the evening may inhibit endogenous melatonin levels. If possible, administration of NSAIDs should be avoided in the evening.

Beta-blockers
Beta-blockers may inhibit the release of endogenous melatonin and should therefore be administered in the morning.

CYP1A inhibitors
Concomitant administration of melatonin with CYP1A2 inhibitors such as fluvoxamine, quinolones, cimetidine, and 5- and 8-methoxypsoralen (5- and 8-MOP) may lead to increased melatonin exposure by inhibiting melatonin metabolism.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from human clinical studies supporting the use of exogenous melatonin during pregnancy. Animal studies are inconclusive with respect to effects on pregnancy, embryonal/fetal development, parturition and postnatal development (see section 5.3). Exogenous melatonin easily crosses the human placenta. Due to the lack of clinical data, treatment with melatonin is not recommended during pregnancy or in women of childbearing potential not using contraceptives.

Breast-feeding
Data from animal studies have shown maternal transfer of melatonin to the fetus via the placenta or in milk. Endogenous melatonin has also been measured in breast milk from lactating women and it is likely that exogenous melatonin also is excreted in breast milk. Melatonin is therefore not recommended for breast-feeding women.

Fertility
No adequate data on the effect of melatonin on human fertility are available. Animal studies are insufficient with respect to fertility. High doses of melatonin and use for longer periods than indicated may impair fertility in humans.

4.7 Effects on ability to drive and use machines

Melatonin has moderate influence on the ability to drive and use machines. Melatonin may cause drowsiness and the product should therefore be used with caution if it is likely that the drowsiness may be associated with a safety risk.

4.8 Undesirable effects

Summary of the safety profile
Melatonin causes few and no serious side effects in the short term, up to three months. Long-term effects are poorly studied. Reported side effects of melatonin are mainly headache, nausea and fatigue in both adults and children. However, these adverse reactions are also common for placebo-treated patients in reported clinical studies and there is no significant difference between patients receiving active substance and placebo in these studies.

No very common side effects have been reported.

Adverse reactions in adults compiled according to MedDRA system organ class are presented within each frequency range as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000); Not known (frequency cannot be estimated from the available data).

System organ class	Common	Uncommon	Rare	Not known
Infections and infestations			herpes zoster	
Blood and lymphatic system disorders			leukopenia, thrombocytopenia	
Immune system disorders				hypersensitivity reaction
Metabolism and nutrition disorders			hypertriglyceridemia, hypocalcaemia, hyponatremia	hyperglycaemia
Psychiatric disorders		irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety	altered mood, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening,	

			libido increased, depressed mood, depression	
Nervous system disorders	headache, somnolence	migraine, lethargy, psychomotor hyperactivity, dizziness	syncope, memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, paresthesia	
Eye disorders			Visual acuity reduced, vision blurred, lacrimation increased	
Ear and labyrinth disorders			Vertigo positional, vertigo	
Cardiac disorders			angina pectoris, palpitations	
Vascular disorders		hypertension	hot flushes	
Gastrointestinal disorders		abdominal pain, upper abdominal pain, dyspepsia, mouth ulceration, dry mouth, nausea	gastroesophageal reflux disease, gastrointestinal disorder, oral mucosal blistering, tongue ulceration, gastrointestinal upset, vomiting, bowel sounds abnormal, flatulence, salivary hypersecretion, halitosis, abdominal discomfort, gastric disorder, gastritis	
Hepatobiliary disorders		hyperbilirubinemia		
Skin and subcutaneous tissue disorders		dermatitis, night sweats, pruritus, rash, pruritus generalized, dry skin	eczema, erythema, hand dermatitis, psoriasis, rash generalized, rash pruritic, nail disorders	angioedema, oedema oral, oedema tongue
Musculoskeletal system and connective tissue disorders		pain in the extremities;	arthritis, muscle spasms, neck pain, night cramps	
Renal and urinary disorders		glycosuria, proteinuria	polyuria, haematuria, nocturia	
Reproductive system and breast disorders		menopausal symptoms	priapism, prostatitis	galactorrhoea
General disorders and/or administration site symptoms		asthenia, chest pain	fatigue, pain, thirst	
Investigations		liver function test abnormal, weight increase	Hepatic enzyme increased, blood electrolytes abnormal,	

			laboratory test abnormal	

Paediatric population
In the paediatric population, a low frequency of generally mild adverse reactions has been reported. The side effects have not been significantly different in children who received placebo compared to children who received melatonin. The most common side effects were headache, hyperactivity, dizziness and abdominal pain. No serious side effects have been observed.

Reporting of suspected adverse reactions
It is important to report suspected side effects after authorisation of the medicinal product. It makes it possible to continuously monitor the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed Appendix V*.

4.9 Overdose

Drowsiness, headache, dizziness and nausea are the most commonly reported signs and symptoms of oral melatonin overdose.

Daily doses of 20 - 50 mg as well as 300 mg for up to 2 years without any clinically significant adverse reactions have been reported in the literature.

A dose of 250 mg taken 4 times daily for 25 - 30 days has only been reported to cause drowsiness/sleepiness. In several cases of reported overdose, mild to moderately severe somnolence was the most reported adverse reaction.

After doses of 3.0 - 6.6 grams for 15 - 36 days, 6 of 11 patients reported daytime somnolence and 4 of 11 patients reported abdominal cramps, diarrhea, or migraine headaches.

Clearance of the active substance is expected within 12 hours of ingestion. Physicians should assess whether standard overdose measures should be applied. No special treatment is required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and sedatives, melatonin receptor agonists, ATC code: N05CH01.

Melatonin is a hormone produced by the epiphysis. It is structurally related to serotonin. Melatonin secretion increases shortly after dark, reaching its peak between 2:00 a.m. and 4:00 a.m. and decreases in the latter half of the night. Melatonin is involved in the control of circadian rhythm and adaptation to the light-dark cycle. Melatonin is also associated with a sedative effect and an increased propensity for sleep.

Mechanism of action
The activity of melatonin at MT1, MT2 and MT3 receptors is thought to contribute to its effect on sleep because these receptors (especially MT1 and MT2) are involved in the regulation of circadian rhythm and sleep.

Pharmacodynamic effect
Melatonin has a sleep and soothing effect and increases the tendency to fall asleep. If melatonin is administered earlier or later than the nocturnal peak secretion of melatonin, the circadian rhythm of melatonin secretion may be earlier or delayed. Administration of melatonin at bedtime (between 22:00 and 00:00) at the destination following rapid transmeridian travel (aircraft flight) accelerates the

conversion of the circadian rhythm from "departure time" to "arrival time" and alleviates the symptoms known as jet lag that follow such a disruption of the circadian rhythm.

Clinical efficacy and safety
Typical symptoms of jet lag are sleep disturbances, daytime sleepiness and fatigue, but mild cognitive symptoms, irritability and gastrointestinal disorders may also occur.

Jet lag gets worse the more time zones are crossed and usually gets worse after traveling east. Eight out of ten clinical trials found that melatonin, taken in conjunction with the time of scheduled bedtime at the destination (10 p.m. to midnight), reduced jet lag after flights crossing five or more time zones. The advantage is likely to be greater the more time zones are passed and smaller for westbound flights. Daily doses of melatonin between 0.5 and 5 mg are equally effective, except that people fall asleep faster and sleep better after 5 mg than 0.5 mg.

In clinical trials, melatonin has been found to reduce overall patient-assessed symptoms of jet lag by approximately 44 % and shorten the duration of jet lag. In two studies of flights across 12 time zones, melatonin effectively reduced jet lag duration by approximately 33 %. Taking melatonin at the wrong time carries a risk that the medicinal product has no effect or has a negative impact on the conversion of the circadian rhythm after jet lag. Therefore, melatonin should not be taken before 20:00 or after 04:00 destination time.

Paediatric population
Treatment with melatonin was investigated in a 4-week randomised, double-blind, placebo-controlled study in 105 children between 6 and 12 years of age diagnosed with ADHD and chronic insomnia. Participants received melatonin (3 mg at body weight < 40 kg [n = 44]; or 6 mg at body weight > 40 mg [n = 9]) immediate-release tablets or placebo.

Mean actigraphic estimation of time to sleep showed an improvement of 26.9 ± 47.8 minutes with melatonin in contrast to placebo where sleep onset was delayed by 10.5 ± 37.4 minutes ($p < 0.0001$). 48.8 % of children receiving melatonin showed an improvement in time to sleep > 30 minutes compared to 12.8 % with placebo ($p = 0.001$). Mean total sleep time improved by 19.8 ± 61.9 minutes with melatonin and decreased by 13.6 ± 50.6 minutes with placebo ($p = 0.01$). In comparison with placebo, the melatonin group showed a decrease in sleep latency ($p = 0.001$) and improved sleep efficiency ($p = 0.01$). Mean sleep onset score was reduced by 1.2 ± 1.3 points (35.3 % from baseline) with melatonin and by 0.1 ± 0.8 points (4.3 % from baseline) with placebo ($p < 0.0001$).

5.2 Pharmacokinetic properties

Absorption
Oral melatonin is almost completely absorbed in adults. Due to a high first-pass metabolism, bioavailability is relatively low and variable in the order of approximately 15 % (range 1 – 56 %). The maximum concentration of orally administered melatonin occurs after 15 - 90 minutes (median T_{max} = 52 min).

The maximum concentration and exposure of melatonin after oral dosing increases proportionally to the dose from 0.25 up to 10 mg.

Data on the effect of ingestion of food at or around the time of intake of melatonin on its pharmacokinetics are limited but suggest that concomitant food intake may increase absorption almost 2-fold. Food intake appears to have a limited effect on the T_{max} of immediate-release melatonin. This is not expected to affect the efficacy or safety of {Invented name}.

Distribution
The plasma protein binding of melatonin in vitro is approximately 60 %. The volume of distribution during the terminal elimination phase is proportional to body weight, averaging just over 1 l/kg.

Metabolism

Melatonin is eliminated mainly by hydroxylation to 6-hydroxymelatonin in the liver, mainly mediated by CYP1A2 (to a lesser extent by CYP1A1). Quantitatively less important O-demethylation to N-acetyl-5-hydroxytryptamine mediated by CYP2C19 occurs. Melatonin metabolites are eliminated mainly in the urine, around 90 % as sulphate and glucuronide conjugates of 6-hydroxymelatonin. Less than 1 % of a melatonin dose is excreted unchanged in the urine.

Elimination
The plasma half-life ($t_{1/2}$) is about 45 minutes (the normal range is around 30 - 60 minutes) in healthy adults. The half-life is on average comparable or slightly shorter in children compared to adults. The once-daily dosing in combination with the short half-life means minimal accumulation of melatonin with regular treatment.

Special groups of patients

Elder
A comparative study of serum melatonin with and without exogenous supplementation found lower concentrations in moderately older adults without treatment, while a tendency for higher concentrations was observed compared to healthy younger adults after treatment. The difference was not statistically significant; The same dosage can be recommended for moderately older people as for younger adults.

Hepatic impairment
Limited data indicate that daytime endogenous melatonin concentrations are significantly elevated in patients with cirrhosis of the liver, probably due to decreased clearance (metabolism) of melatonin. The serum $t_{1/2}$ for exogenous melatonin in patients with cirrhosis was twice as high as that of controls in a small study. Since melatonin is primarily metabolized in the liver, hepatic impairment can be expected to lead to increased exposure to exogenous melatonin.

Renal impairment
No studies have been conducted on the pharmacokinetics of melatonin in any type of renal impairment, see section 4.2 Special populations.

5.3 Preclinical safety data

Preclinical data show no special hazard for humans based on repeated dose toxicity or genotoxicity studies.

Data on reproductive toxicology are limited. A study in pregnant rats did not show direct or indirect harmful effects with respect to pregnancy, fetal survival or fetal development.

Data from animal studies suggest transmission of melatonin to the fetus via the placenta and to breast milk.

Safety studies in juvenile animals are lacking.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol (E 422)
Potassium sorbate (E 202)
Hydrochloric acid (for pH adjustment)
Methyl parahydroxybenzoate (E 218)
Water, purified

6.2 Incompatibilities

Not relevant.

6.3 Shelf life

30 months. Shelf life after first opening: 6 months.

6.4 Special precautions for storage

Store in the original bottle in order to protect from light.

6.5 Nature and contents of container

Amber glass bottle of 100 ml, with a white cap of aluminium. An oral polyethylene/polystyrene dosing syringe is included in the carton with the bottle. The size of the syringe is 5 ml with a graduation scale of 0.1 ml.

6.6 Special precautions for disposal

No special instructions for destruction.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<to be completed nationally>

8. MARKETING AUTHORISATION NUMBER

<to be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2023-04-25

10. DATE OF REVISION OF THE SUMMARY OF PRODUCT CHARACTERISTICS

28-NOV-2025