SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Melatonin Evolan 1 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml oral solution contains 1 mg melatonin.

Excipients with known effect:
Benzyl alcohol 6 mg/ml
Propylene glycol 52 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.
Clear, pale yellow to yellow coloured solution with strawberry taste.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Adults with jet lag
The recommended dose is 1-5 mg (1-5 ml) and should be taken at bedtime, for 4-7 days.
The dose may be increased up to 5 mg (5 ml) if symptoms are not sufficiently relieved at lower doses.

The first dose should be taken on arrival at the destination, at the usual bedtime.
Due to the potential for incorrectly timed intake of melatonin to have no effect, or an adverse effect, on re-synchronisation following jet lag, Melatonin Evolan should not be taken before 20:00 or after 04:00 at destination.

A maximum of 16 treatment cycles of jet lag with Melatonin Evolan may occur per year.

Insomnia in children and adolescents with ADHD
The treatment must be initiated by physicians with experience in ADHD and/or the treatment of sleep disorders in children.
The standard dose is 1-2 mg (equivalent to 1-2 ml) 30 to 60 minutes before bedtime.
The dose of melatonin can be increased by 1 mg (1 ml) per week until an effect is achieved to a maximum of 5 mg (5 ml) daily, 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 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 Evolan 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.

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

Special populations

Elderly
As the pharmacokinetics of melatonin (immediate release) is comparable in young adults and elderly persons in general, no specific dosage recommendations for elderly persons are provided (see section 5.2).

Renal impairment
The effect of melatonin in patients with impaired renal function. has not been studied. Caution should be exercised when melatonin is administered to such patients. Melatonin Evolan is not recommended for patients with severe renal impairment (see section 5.2).

Hepatic impairment
There are no studies on the use of melatonin in patients with hepatic impairment. Published data show markedly elevated endogenous melatonin levels in patients with hepatic impairment. Therefore, Melatonin Evolan is not recommended for patients with moderate or severe hepatic impairment (see section 5.2).

Children below 6 years of age
Melatonin Evolan is not recommended for children below 6 years with ADHD.

Method of administration
Oral use.

Food can increase the plasma concentration of melatonin (see section 5.2). Taking melatonin with carbohydrate-rich meals may impair blood glucose control for several hours (see section 4.4).

Alcohol should be avoided while using Melatonin Evolan (see section 4.5).

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

Drowsiness
Melatonin can cause drowsiness. Therefore, Melatonin should be used with caution if the effects of drowsiness are likely to be associated with a safety risk.

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 should be exercised 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 clinical data regarding use of melatonin in patients with autoimmune diseases. Therefore, melatonin is not recommended in patients with autoimmune diseases.

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.

Melatonin Evolan contains propylene glycol and benzyl alcohol
This medicine contains 52 mg propylene glycol in each ml and 6 mg benzyl alcohol in each ml. Benzyl alcohol may cause allergic reactions. High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults. Melatonin is metabolized mainly via the enzyme CYP1A2. Therefore, interactions between melatonin and other active substances as a consequence of their effect on CYP1A enzymes are possible.

Pharmacokinetic interactions

Fluvoxamine
Caution should be exercised in patients on fluvoxamine, which increases melatonin levels (by 17-fold higher AUC and a 12-fold higher serum C_{max}). The combination should be avoided.

5- or 8-methoxypsoralen
Caution should be exercised in patients on 5- or 8-methoxypsoralen (5 and 8-MOP), which increases melatonin levels by inhibiting its metabolism.

Cimetidine
Caution should be exercised in patients on cimetidine, which is a weak inhibitor of CYP1A2. Cimetidine has been reported to increase plasma concentrations of melatonin.

Estrogens
Estrogens have been shown to increase melatonin concentrations by inhibiting CYP1A1 and CYP1A2 (4-5 fold increase in melatonin concentrations when used in combination with combined hormonal contraceptives). Caution must be exercised in patients treated with estrogens (e.g. hormonal contraceptive combinations or hormonal substitution therapy).

CYP 1A inhibitors
CYP1A2 inhibitors, such as quinolones, may lead to increased melatonin exposure.

Caffeine
Caffeine is a substrate for CYP1A2. Caffeine has been shown to increase serum concentrations of orally administered melatonin (2.2-fold higher AUC and 2.4-fold higher C_{max}).

CYP1A2 inducers
CYP1A2 inducers, such as carbamazepine and rifampicin, may result in reduced plasma concentrations of melatonin.

Smoking
Cigarette smoking may decrease melatonin levels due to induction of CYP1A2.

Pharmacodynamic interactions

Alcohol
Alcohol should not be taken with melatonin, as this combination may reduce the effect of melatonin on sleep.

Benzodiazepine-like hypnotics
Melatonin may enhance the sedative properties of benzodiazepine and non-benzodiazepine hypnotics such as zaleplon, zolpidem and zopiclone. Concomitant treatment with melatonin should be avoided.

Nifedipine
Melatonin may reduce the hypotensive effect of nifedipine. Caution should be exercised in concomitant treatment with melatonin and dose adjustment of nifedipine may be needed. As it is not known whether this is a class effect, caution should also be exercised when combining melatonin with other calcium antagonists.

Warfarin
Case reports have reported that patients treated with melatonin and warfarin received concurrent changes in INR and prothrombin time. The combination of warfarin or other vitamin K antagonists with melatonin may require dose adjustment of the anticoagulant drugs and should be avoided.

NSAID
Prostaglandin synthesis inhibitors (NSAIDs) such as acetylsalicylic acid and ibuprofen in the evening can inhibit endogenous melatonin levels during the early part of the night by up to 75 percent. If possible, administration of NSAIDs should be avoided in the evening.

Beta blockers
Beta blockers can inhibit nocturnal release of endogenous melatonin, and should therefore be administered in the morning.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data for the use of melatonin in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Exogenous melatonin readily crosses the human placenta. Melatonin Evolan is not recommended during pregnancy or in women and adolescents of childbearing potential not using contraception.

Breastfeeding
There is insufficient data on the excretion of melatonin/metabolites in human milk. Endogenous melatonin is secreted in human milk. A risk for the breastfed child cannot be excluded as data are missing. Melatonin Evolan is therefore not recommended for women who are breastfeeding.

Fertility
There is limited clinical data about effects of melatonin on fertility. Animal studies are insufficient with respect to effects on fertility.

4.7 Effects on ability to drive and use machines

Melatonin Evolan has moderate influence on the ability to drive and use machines. Melatonin may cause drowsiness and may decrease alertness for several hours, therefore use of Melatonin Evolan is not recommended prior to driving and using machines.

4.8 Undesirable effects

Summary of the safety profile

Drowsiness/sleepiness, headache, and dizziness/disorientation are the most frequently reported adverse reactions when melatonin is taken on a short-term basis to treat jet-lag and primary insomnia. Drowsiness, headache, dizziness, and nausea are also the adverse reactions reported most frequently when typical clinical doses of melatonin have been taken for periods of several days to several weeks, by healthy persons and patients.

Tabulated list of adverse reactions

The reported side effect frequencies are based on the following categories:
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 (cannot be established from the available data).

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Rare	Herpes zoster
Blood and lymphatic system disorders	Rare	Leucopenia, thrombocytopenia
Immune system disorders	Not known	Hypersensitivity reaction
Metabolism and nutrition disorders	Rare	Hypertriglyceridaemia, hypocalcaemia, hyponatraemia
	Not known	Hyperglycaemia
Psychiatric disorders	Uncommon	Irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety
	Rare	Mood altered, aggression, agitation, crying, disorientation, early morning awakening, libido increased, depressed mood, depression
Nervous system disorders	Common	Headache, somnolence
	Uncommon	Migraine, lethargy, psychomotor hyperactivity, dizziness
	Rare	Syncope, memory impairment, disturbance in attention, restless legs syndrome, poor quality sleep, paraesthesia
Eye disorders	Rare	Visual acuity reduced, vision blurred, lacrimation increased
Ear and labyrinth disorders	Rare	Vertigo positional, vertigo
Cardiac disorders	Rare	Angina pectoris, palpitations
Vascular disorders	Uncommon	Hypertension
	Rare	Hot flush
Gastrointestinal disorders	Uncommon	Abdominal pain, abdominal pain upper, dyspepsia, mouth ulceration, dry mouth, nausea
	Rare	Gastro-esophageal 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	Uncommon	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis, night sweats, pruritus, rash, dry skin
	Rare	Eczema, erythema, hand dermatitis, psoriasis, rash generalised, rash pruritic, nail disorder
	Not known	Angioedema, tongue oedema, oedema of mouth
Musculoskeletal and connective tissue disorders	Uncommon	Pain in extremity
	Rare	Arthritis, muscle spasms, neck pain, night cramps
Renal and urinary disorders	Uncommon	Glycosuria, proteinuria
	Rare	Polyuria, haematuria, nocturia

Reproductive system and breast disorders	Uncommon	Menopausal symptoms
	Rare	Priapism, prostatitis
	Unknown	Galactorrhoea
General disorders and administration site conditions	Uncommon	Asthenia, chest pain
	Rare	Fatigue, pain, thirst
Investigations	Uncommon	Liver function test abnormal, weight increased
	Rare	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 adverse reactions have not been significantly different in children who has received placebo compared to children who received melatonin. The most common adverse reactions were headache, hyperactivity, vertigo and abdominal pain. No serious adverse reactions have been observed.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Drowsiness, headache, dizziness, and nausea are the most commonly reported signs and symptoms of overdose with oral melatonin.
Administration of daily doses of up to 300 mg melatonin without any clinically significant side effects has been reported in the literature.

Flushes, abdominal cramps, diarrhoea, headache, and scotoma have been reported after ingestion of extremely high melatonin doses (3000 – 6600 mg) for several weeks.

General supportive measures should be employed. Gastric lavage and administration of activated charcoal can be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, melatonin receptor agonists, ATC code: N05CH01

Melatonin is a naturally occurring hormone produced by the epiphysis and structurally related to serotonin. Physiologically, melatonin secretion rises shortly after dark, reaching its peak between 02:00 and 04:00 in the morning and decreases during the latter half of the night. Melatonin is associated with control of the circadian rhythm and adaptation to the light-dark cycle.

Mechanism of action
The activity of melatonin on MT1 and MT2 receptors is thought to contribute to its sleep-promoting properties, as these receptors are involved in the regulation of circadian rhythms and sleep regulation.

Pharmacodynamic effects
Melatonin has a hypnotic/sedative effect and increases propensity for sleep. Melatonin administered earlier or later than the nocturnal peak in melatonin secretion can, respectively, advance or delay the circadian rhythmicity of melatonin secretion. Administration of melatonin at bedtime (between 22:00 and 24:00 hr) at destination following rapid transmeridian travel (aircraft flight) hastens

resynchronisation of circadian rhythmicity from 'departure time' to 'destination time', and ameliorates the collection of symptoms known as jetlag that are a consequence of such de-synchronisation.

Clinical efficacy and safety
Typical symptoms of jet lag are sleep disturbances, daytime tiredness and fatigue, though mild cognitive impairment, irritability, and gastrointestinal disturbances also may occur. Jet lag is worse the more time-zones crossed and is typically worse following eastward travel.

Clinical trials have shown that melatonin, when taken near bedtime local time (22:00 to midnight), decreases jet lag on flights crossing 5 or more time zones. The benefit is likely to be greater the more time zones are crossed, and less for westward flights.

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. These same adverse reactions, plus nausea, are those typically associated with short-term use of melatonin in reviews of the safety of melatonin in humans.

Paediatric population
Melatonin treatment has been studied in a 4-week randomized, double-blind, placebo-controlled study conducted in 105 children between 6-12 years of age, with ADHD and chronic sleep onset insomnia (van der Heijden KB et al. 2007). Participants received melatonin in immediate release tablets (3 mg when body weight <40 kg [n= 44]; or 6 mg when body weight >40 kg [n = 9]) or placebo.

Mean actigraphic estimate of sleep onset advanced by 26.9 ± 47.8 minutes with melatonin, whereas there was a delay of 10.5 ± 37.4 minutes with placebo ($p < 0.0001$). 48.8% of children who received melatonin showed an advance of sleep onset >30 minutes compared to 12.8% with placebo ($p =0.001$). There was an increase in mean total time asleep of 19.8 ± 61.9 minutes with melatonin and a decrease of 13.6 ± 50.6 minutes with placebo ($p = 0.01$). As compared with placebo, the melatonin group showed a decrease in sleep latency ($p = 0.001$) and increase in sleep efficiency ($p = 0.01$). The mean score on sleep log item difficulty falling asleep decreased by 1.2 ± 1.3 points (35.3% of baseline) with melatonin and by 0.1 ± 0.8 points (4.3% of baseline) with placebo ($p < 0.0001$).

There was no significant effect on behaviour, cognition, and quality of life. There were no discontinuations or withdrawals caused by adverse events.

5.2 Pharmacokinetic properties

Melatonin is a small, amphiphilic molecule (molecular weight 232 g/mol) active in its parent form. Data summarised below are from studies that generally involved healthy men and women, primarily young and middle-aged adults.

Absorption
Orally administered melatonin is almost completely absorbed. Due to high first-pass metabolism, bioavailability is in the order of 15% (range 1-56%). A 3 mg dose of Melatonin Evolan oral solution raises the C_{max} of plasma melatonin to ~ 7200 pg/ml with a T_{max} of about 24 minutes, although C_{max} shows considerable inter-individual variability.

Based on limited data, with high inter-subject variability, food intake may increase the exposure and peak plasma concentration of melatonin, although probably not to a clinically relevant extent.

Distribution
The in vitro plasma protein binding of melatonin is estimated to be 60–80%. Melatonin primarily binds to albumin, but also to alpha-1-glycoprotein; binding to other plasma proteins is limited. Melatonin is rapidly distributed from plasma, and easily crosses the blood-brain barrier. Melatonin easily crosses placenta.

Biotransformation
Elimination of melatonin occurs mainly via metabolism in the liver, mainly through hydroxylation to 6-hydroxymelatonin, mainly mediated by CYP1A2 (to a lesser extent by CYP1A1). Quantitatively less important O-demethylation to N-acetyl-5-hydroxytryptamine mediated by CYP2C19 occurs. The melatonin metabolites are mainly eliminated via 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
Plasma elimination half-life (T½) is ~ 45 minutes (normal range ~ 30 – 60 minutes) in healthy adults. The half-life is on average comparable or slightly shorter in children compared to adults.

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

Gender
Higher exposure and maximum plasma concentrations have been reported in women compared to men who have received melatonin orally, however a large variability in the pharmacokinetics is observed. Plasma melatonin half-life does not appear to be significantly different in men and women. Dose adjustment for women is not necessary.

Special populations

Elderly
In a comparative study of the levels of serum melatonin with and without administration of exogenous melatonin, lower concentrations were found in moderately older adults without treatment, while a trend toward higher concentrations was observed compared to healthy younger adults after treatment. The observed difference between the age groups was not statistically significant, the same dose of melatonin can be recommended to moderately older adults and younger adults.

Hepatic impairment
Limited data indicate that daytime endogenous blood melatonin concentration is markedly elevated in patients with liver cirrhosis, probably due to reduced clearance of melatonin. Since melatonin is largely eliminated via liver metabolism, exposure to exogenous melatonin is likely to be higher in patients with hepatic impairment (see section 4.2).

Renal impairment
The effect of renal impairment on the pharmacokinetics of melatonin administered has not been studied. However, published data show elevated endogenous melatonin levels in patients with chronic renal failure (see section 4.2).

5.3 Preclinical safety data

Current studies on safety pharmacology, general toxicity, genotoxicity and carcinogenicity, did not show any particular risks to humans.

In toxicological studies, effects were seen only at high exposures/at exposures significantly higher than clinical exposures. These effects are therefore considered to have no clinical relevance.

In the reproductive toxicology studies, oral administration of melatonin to pregnant female rats did not lead to any effects on the offspring, with regard to fetal survival, skeletal and visceral anomalies or birth weight. Administration of melatonin to mice early in their pregnancy did not generate any apparent reproductive toxicities.

There are no safety studies in juvenile animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water
Sucralose (E955)
Benzyl alcohol
Sodium ascorbate
Propylene glycol (E1520)
Strawberry flavour.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months
After first opening: 3 months

6.4 Special precautions for storage

Store below 25°C.
Store opened package below 25°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Brown glass bottle with screw cap (polyethylene) and a funnel (polyethylene). A 5 ml dosing spoon (polypropylene) graduated 1-2-3-4-5 ml is also provided.
Package sizes: 100 ml, 150 ml and 200 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2025-06-05

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