SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Melatonin Aspire 1 mg/mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of solution contains 1mg of melatonin.

Excipient with known effect:
Each mL of solution contains 1mg methyl parahydroxybenzoate (E218), see section 4.4.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Clear colourless to slightly yellow solution.

4. Clinical particulars

4.1 Therapeutic indications

<Invented name> is indicated for:

- Short-term treatment of jet lag in adults.
- Sleep onset insomnia in children and adolescents aged 6-17 years with attention deficit hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient.

4.2 Posology and method of administration

Posology

Short-term treatment of jet lag in adults
The standard dose is 1-5 mg (1-5 mL) daily for a maximum of 5 days. The dose that adequately alleviates symptoms should be taken for the shortest period.

The first dose should be taken on arrival at destination at the habitual bed-time.

Due to the potential for incorrectly timed intake of melatonin to have no effect, or an adverse effect, on resynchronisation following jet-lag, This medicine should not be taken before 20:00 hr or after 04:00 hr at destination.

Insomnia in children and adolescents aged 6-17 years with attention deficit hyperactivity disorder

Treatment should be initiated by physicians experienced in ADHD and/or paediatric sleep medicine.

The recommended starting dose is 1-2 mg (1-2 mL), 30-60 minutes before bedtime.

The dose of melatonin should be individually adjusted by increasement of 1 mg (1 ml) every week until effective, up to a maximum of 5 mg per day, independent of age. The lowest effective dose should be sought and taken for the shortest period.

Limited data are available for up to 3 months of treatment and there is very limited data beyond that. In any case, the physician should assess the treatment effect at regular intervals and consider discontinuing treatment if a clinically significant treatment effect has not been achieved. The patient should be monitored at regular intervals to check that <invented name> is still the most appropriate treatment.
During ongoing treatment, especially if the treatment effect is uncertain, attempts at discontinuation should be made regularly.

If insomnia has occurred during treatment with ADHD medication, dose adjustment or change of ADHD medication should be considered.

Children
The safety and efficacy of (Invented name) in children and adolescents have not been established for the indication jet-lag.

The safety and efficacy of (Invented name) in children aged 0 – 6 years with ADHD have not been established.

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 any degree of renal impairment on the pharmacokinetics of melatonin has not been studied. Published data show elevated endogenous melatonin levels in patients with chronic renal failure. Caution should be exercised if melatonin is used by patients with renal impairment.

Hepatic impairment
There are no known studies on the use of melatonin in patients with hepatic impairment. Published data show markedly elevated endogenous melatonin levels in patients with hepatic impairment. This medicine is not recommended in patients with hepatic impairment (see sections 4.4 and 5.2).

Method of administration
<invented name> is for oral use only. A 10 ml graduated oral syringe with intermediate graduations of 0.5 ml and a “Press-In” Bottle Adapter (PIBA) are provided with the product.

1. Open the bottle and at first use, insert the “Press-In” Bottle Adapter (PIBA).

2. Insert the syringe into the PIBA and draw out the required volume from the inverted bottle.

3. Remove the filled syringe from the bottle in the upright position

4. Discharge the syringe contents slowly into the mouth and swallow the medicine.

5. Rinse the syringe and replace the cap on the bottle (PIBA remains in place).

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 may cause drowsiness and should be used with caution if the effects of drowsiness are likely to be associated with a risk to patient safety.

Epilepsy

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

Immunological diseases

Occasional case reports have described exacerbation of an autoimmune disease in patients taking melatonin. There is no data regarding use of this medicine in patients with autoimmune diseases. <Invented name> 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. <Invented name> should be taken at least 2 hours before or at least 2 hours after a meal; ideally at least 3 hours after meal by persons with significantly impaired glucose tolerance or diabetes,

This medicinal product contains methyl parahydroxybenzoate
This may cause an allergic reaction (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Pharmacokinetic interactions
Melatonin is metabolised mainly by the hepatic cytochrome P450 CYP1A enzymes, primarily CYP1A2. Therefore, interactions between melatonin and other active substances as a consequence of their effect on CYP1A enzymes are possible.

CYP1A2 inhibitors

- Fluvoxamine is a potent inhibitor of CYP1A2 and to a lesser extent CYP2C. Fluvoxamine has been shown to increase serum concentration of orally administered melatonin (17-fold higher AUC and 12-fold higher serum Cmax). This combination should be avoided.

- Caution is indicated in patients taking 5- or 8-methoxypsoralen (5 or 8-MOP), since this agent increases melatonin levels by inhibiting its metabolism.

- Caution is indicated in patients taking cimetidine, since this agent increases plasma melatonin levels by inhibiting its metabolism by CYP2D.

- Caution should be exercised in patients receiving oestrogen therapy (e.g. in the form of contraceptives or hormone replacement therapy), since estrogens increase melatonin levels 4 to 5 fold by inhibiting its metabolism, primarily via inhibition of CYP1A2.

- CYP1A2 inhibitors (such as quinolones) may increase systemic melatonin levels.

- 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 Cmax).

CYP1A2 inducers

- CYP1A2 inducers (such as carbamazepine, phenytoin and rifampicin) may reduce plasma concentrations of melatonin through an increase in melatonin metabolism. Dose adjustment may be needed..

- Cigarette smoking may decrease melatonin levels due to induction of CYP1A2. The metabolism of melatonin may be induced by smoking, which may lead to reduced melatonin concentrations. The melatonin AUC were significantly lower during smoking compared to after smoking abstinence (2.9-fold lower AUC).

Pharmacodynamic interactions

Adrenergic agonists/antagonists, opiate agonists/antagonists, antidepressants, prostaglandin inhibitors, tryptophan and alcohol affect the endogenous secretion of melatonin in the epiphysis, but do not affect the metabolism of melatonin. It is not known if these interactions are of clinical significance.

Alcohol
Alcohol should not be used concomitantly with melatonin since it may reduce the effect of melatonin on sleep (see section 4.2)

Nifedipine
Melatonin may reduce the hypotensive effect of nifedipine, so caution should be exercised in this combination and dose adjustment of nifedipine may be needed. As it is not known if this is a class effect, caution should be exercised when combining melatonin and other calcium antagonists.

Warfarin
It has been reported in case reports that concomitant use of melatonin and vitamin K antagonists such as warfarin can lead to either increased or decreased prothrombin levels, and a 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 anticoagulant drugs and should be avoided.

Benzodiazepine-related hypnotics
Melatonin may enhance the sedative properties of benzodiazepine and non-benzodiazepine hypnotics such as zaleplon, zolpidem and zopiclone. In a clinical study, there was clear evidence of a transient pharmacodynamic interaction between melatonin prolonged-release tablet and zolpidem one hour after concomitant dosing. Concomitant administration led to an increased reduction in attention, memory and coordination compared to zolpidem alone.

NSAIDs

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

Beta-blockers
Beta-blockers may suppress the 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. {Invented name} is not recommended during pregnancy or in women of childbearing potential not using contraception.

Breast-feeding
Endogenous melatonin is found in human breast thus it can be assumed that exogenous melatonin is excreted in human milk. A risk to the breastfed child cannot be excluded. {Invented name} should not be used during breast-feeding.

Fertility
There is very limited clinical data about effects of melatonin on fertility. Animal studies are insufficient with respect to effects on fertility (see Section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
Melatonin causes few to no serious adverse reactions in the short term, up to three months. Drowsiness/sleepiness, headache, and dizziness/ disorientation are the most frequently reported adverse effects when melatonin is taken on a short-term basis to treat jet-lag. Drowsiness, headache, dizziness and nausea are also the adverse effects 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.

There is limited documentation of long-term treatment with melatonin.

The following adverse reactions to melatonin in general have been reported in clinical trials or spontaneous case reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1000 to <1/100); Rare (≥1/10000 to <1/1000); Very rare (<1/10000); Not known (cannot be established from the available data).

System Organ Class	Very Common	Common	Uncommon	Rare	Not known

Blood and lymphatic system disorders				Leukopenia, thrombocytopenia	
Immune system disorders					Hypersensitivity reaction
Metabolism and nutrition disorders				Hypertriglyceridaemia, hyponatremia	Hyperglycaemia
Psychiatric disorders			Irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety	Mood changes, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, increased libido, depressed mood, depression	
Nervous system disorders		Headache, somnolence	Migraine, lethargy, psychomotor hyperactivity, dizziness	Syncope (fainting), memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, paraesthesia	Drowsiness, sedation
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 flush	
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			Hyperbilirubinaemia		
Skin and subcutaneous tissue disorders			Dermatitis, night sweats, pruritus, rash, dry skin	Eczema, erythema, hand dermatitis, psoriasis, generalised rash, pruritic rash, nail disorder	Angioedema, tongue oedema, oedema of the mouth

Musculoskeletal and connective tissue disorders			Pain in 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 administration site conditions			Chest pain, asthenia	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 side effects have been reported. The number of adverse reactions has not differed significantly between children who have received placebo compared to melatonin. The most common adverse reactions were dizziness, headache, gastrointestinal symptoms and increased excitability. 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 or overdose with oral melatonin.

Ingestion of daily doses of up to 300mg of melatonin did not cause clinically significant adverse reactions.

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

Due to the short half-life of melatonin, clearance of the melatonin is expected within 12 hours of ingestion.

General supportive measures should be employed. The administration of activated charcoal can be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Melatonin is a hormone and antioxidant. Melatonin secreted by the pineal gland is involved in the synchronisation of circadian rhythms to the diurnal light-dark cycle. Melatonin secretion/ plasma melatonin level increases shortly after the onset of darkness, peaks at 2-4 am and declines to the daytime nadir by dawn. Peak melatonin secretion is almost diametrically opposite peak daylight intensity, with daylight being the primary stimulus for maintaining the circadian rhythmicity of melatonin secretion.

Mechanism of action
The pharmacological mechanism of action in melatonin is believed to be based on its interaction with MT1, MT2 and MT3 receptors, as these receptors (mainly MT1 and MT2) are involved in the regulation of circadian rhythms and sleep regulation in general.

Pharmacodynamic effects
Melatonin has a hypnotic/ sedative effect and increased 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 (bedtime 22:00 and 24:00hr) 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 jet-lag that are a consequence of such de-synchronisation.

Clinical efficacy and safety

Short-term treatment of jet lag in adults.

Typical symptoms of jet-lag are sleep disturbances and daytime tiredness and fatigue, though mild cognitive impairment, irritability, and gastrointestinal disturbances may also occur.

Jet-lag is worse the more time-zones crossed and is typically worse following eastward travel as people generally find it harder to advance their circadian rhythm (body clock) than to delay it, as required following westward travel.

Clinical trials found that melatonin, taken close to the target bedtime at the destination (10 pm to midnight), decreased jet-lag from flights crossing five or more time zones. The benefit is likely to be greater the more time zones are crossed, and less for westward flights. Daily doses of melatonin between 0.5 and 5 mg are similarly effective, except that people fall asleep faster and sleep better after 5 mg than 0.5 mg.

Clinical trials have found melatonin to reduce patient-assessed overall symptoms of jet-lag by ~44%, and to shorten the duration of jet-lag (Petrie 1993). In 2 studies of flights over 12 time zones melatonin effectively reduce the duration of jet-lag by ~33%. Due to the potential for incorrectly timed intake of melatonin to have no effect, or an adverse effect, on re-synchronisation of circadian rhythmicity / jet-lag, melatonin should not be taken before 20:00 hr or after 04:00 hr at destination.

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, dizziness/disorientation and gastrointestinal disorders were the most common events.

Insomnia in children and adolescents aged 6-17 years with attention deficit hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient.

Mean actigraphic estimate of sleep onset advances by 26.9 ± 47.8 minutes, compared to a delay of 10.5 ± 37.4 minutes with placebo ($p < 0.0001$) in a 4-week randomised, double-blind, placebo- controlled study conducted in 105 stimulant-free children of 6 to 12 years, with ADHD and chronic sleep onset insomnia. In the melatonin group an advance of sleep onset >30 minutes was more common (48.8% of children) than in those who received placebo (12.8%, $p = 0.001$). 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.

5.2 Pharmacokinetic properties

Melatonin is a small, amphiphilic molecule (molecular weight 232g/mol) active in its parent form. Melatonin is synthesised in the human body from tryptophan via serotonin. Small quantities are obtained via diet. 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. Oral bioavailability is 9-33%, owing to first pass metabolism of melatonin. Plasma Tmax is 25-60 minutes.

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

Distribution
The protein binding of melatonin is approximately 50 – 60%. Melatonin primarily binds to albumin, though also binds alpha1-acid glycoprotein; binding to other plasma proteins is limited. Melatonin rapidly distributes from the plasma into and out of most tissues and organ, and readily crosses the brain-blood barrier. Melatonin readily crosses the placenta. The level in umbilical blood of full-term babies closely correlates with, and is only slightly lower (~ 15 – 35%) than, that of their mother following ingestion of a 3 mg dose.

Metabolism
Melatonin is mainly metabolised by the liver. Experimental data suggest that the cytochrome P450 enzymes CYP1A1 and CYP1A2 are primarily responsible for melatonin metabolism, with CYP2C19 of minor importance. Melatonin is primarily metabolised to 6-hydroxymelatonin (constituting ~ 80 – 90% of melatonin metabolites recovered in the urine). N-acetylserotonin appears to be the primary minor metabolite (constituting ~ 10% of melatonin metabolites recovered in the urine). Melatonin metabolism is very rapid, with plasma 6-hydroxymelatonin level rising within minutes of exogenous melatonin entering the systemic circulation. 6-hydroxymelatonin undergoes sulphate conjugation (~ 70%) and glucuronide conjugation (~ 30%) prior to excretion.

Elimination
Plasma elimination half-life (T½) is ~ 45 minutes (normal range ~ 30 – 60 minutes) in healthy adults. Melatonin metabolites are mainly eliminated by the urine, ~ 90% as sulphate and glucuronide conjugates of 6-hydroxymelatonin. Less than ~ 1% of a melatonin dose is excreted unchanged in urine. The half-life, on average, is comparable or slightly shorter in children compared to adults.

Linearity

Plasma melatonin Cmax and AUC increase in a directly proportional, linear manner for oral doses or immediate-release melatonin in the range of 0.25-10 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 older adults and younger adults.

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).

As melatonin is primarily excreted as metabolites in the urine, plasma levels of melatonin metabolites can be expected increase in patients with more advanced renal impairment.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of melatonin administered has not been studied. Published data show elevated endogenous melatonin levels in patients with hepatic impairment. Since melatonin is largely eliminated via liver metabolism, exposure to melatonin is likely to be higher in patients with hepatic impairment (see section 4.2).

Serum T½ for exogenous melatonin in cirrhosis patients was double that of controls in a small study. As the liver is the primary site of melatonin metabolism, hepatic impairment can be expected to result in increased exposure to exogenous melatonin.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, mutagenicity, genotoxicity, carcinogenic potential.

Effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

The data regarding reproductive toxicology is limited.

Embryo-foetal development studies in rats and rabbits did not show direct or indirect harmful effects with respect to pregnancy, foetal survival, foetal body weight, or incidences of foetal malformations/variations.

Results from studies of prenatal and postnatal development in rats indicate that melatonin administration affects the hormonal level and sexual maturation in the offspring.

Data from animal studies indicate that melatonin is transmitted to the foetus via the placenta.

There are no safety studies on juvenile animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218)
Potassium sorbate (E202)
Hydrochloric acid (E507) (to adjust pH)
Glycerol (E422)
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above 25°C. Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

The product is supplied as 150 mL oral solution in an amber, type III glass bottle closed with a high-density polyethylene (HDPE) child-resistant closure and tamper-evident screw cap. A low-density polyethylene (LDPE), 10 ml graduated oral syringe with intermediate graduations of 0.5 ml, and an LDPE “press in” syringe/bottle adaptor are also provided.

6.6 Special precautions for disposal

No special requirements for disposal. 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(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

2025-03-21