SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Melatonin SERB 1 mg/mL Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 1 mg of melatonin.

Excipients with known effect:

Propylene glycol (E 1520): 53 mg per 1 ml dose.

Methylparaben (E218): 1.5 mg per 1 ml dose.

Propylparaben (E216): 0.18 mg per 1 ml dose.

Sodium: 0.09 mg per 1 ml dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution.
Clear, colourless to yellowish solution with characteristic strawberry odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Melatonin 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.
- Delayed sleep wake phase disorder (DSWPD) in children and adolescents aged 6-17 years and adults up to 25 years of age, where sleep hygiene measures have been insufficient.
- Single use for short-term sedation under medical supervision to facilitate electroencephalograms (EEG) in children and adolescents from 1 to 18 years.

4.2 Posology and method of administration

Posology

Short-term treatment of jet lag

Adults

The recommended dose is 1 to 5 mg (1 to 5 ml) daily for a maximum of 5 days.

The recommended starting dose is 3 mg (3 ml).

The dose may be increased to 6 mg (6 ml) if the standard dose does not adequately alleviate symptoms. 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 re-synchronisation following jet lag, Melatonin should not be taken before 20:00 hr or after 04:00 hr at destination.

As alcohol can impair sleep and potentially worsen certain symptoms of jet lag (e.g. headache, morning fatigue, concentration) it is recommended that alcohol is not consumed when taking Melatonin (see section 4.5).

Melatonin may be taken for a maximum of 16 treatment periods per year.

Children and adolescents under 18 years of age

The safety and efficacy of melatonin for use in jet lag has not been established in children and adolescent under 18 years.

Sleep onset insomnia in children and adolescents aged 6-17 years with ADHD

Treatment should be initiated by physicians experienced in ADHD and/or paediatric sleep medicine.
The recommended starting dose is 1 to 2 mg (1 to 2 ml) 30-60 minutes before bedtime.

The dose of Melatonin can be increased by 1 mg (1 ml) every week until effect up to a maximum 5 mg (5 ml) per day, independent of age. The lowest effective dose that controls symptoms should be given.

There is insufficient safety data to support long term use of melatonin in children approaching puberty. After at least 3 months of treatment, the physician should evaluate the treatment effect and consider discontinuing the 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 is still the most appropriate treatment. During ongoing treatment, especially if the treatment effect is uncertain, discontinuation attempts should be done regularly at least once per year.

Limited data are available for up to 3 years of treatment (please see section 4.4).If insomnia has occurred during treatment with ADHD medication, dose adjustment or change of treatment should be considered.

Adults

In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood. However, initiation of treatment in adults is not appropriate.

Children under 6 years of age with ADHD

The safety and efficacy of Melatonin in children aged 0-6 years have not been established.

Delayed sleep wake phase disorder In children and adolescents (6-17 years) and adults up to 25 years of age

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

The recommended starting dose is 1 to 2 mg once every day, 1 to 2 hours before the fixed desired bedtime, given as 1 to 2 ml of Melatonin.

The dose of Melatonin should be adjusted individually until effect up to a maximum of 5 mg per day, independent of age. The lowest effective dose that controls symptoms should be givenand taken for the shortest period.

After 6 weeks of treatment, the physician should evaluate the treatment effect and consider discontinuing the treatment if no clinically relevant treatment effect is seen. In patients with significant continuing daytime sleepiness or misaligned circadian rhythm the possibility of high residual melatonin in the morning should be considered. In these cases, melatonin can be stopped and restarted at a lower dose. The dose that adequately alleviates symptoms should be taken for the shortest period.

There is insufficient safety data to support long term use of melatonin in children approaching puberty. After the achievement of advanced sleep-wake phase for 6 weeks, treatment should be stopped to evaluate if the patient can independently maintain an advanced sleep-wake schedule. If withdrawal of melatonin results in clinical relapse, melatonin can be resumed and continued.

Limited data are available for up to 3 years of treatment (please see section 4.4).

Adults over 25 years of age

In adults whose symptoms persist past the age of 25 and who have shown clear benefit from treatment, it may be appropriate to continue treatment. However, initiation of treatment in adults over 25 years of age is not appropriate.

Children under 6 years of age with DSWPD

The safety and efficacy of Melatonin in children aged 0-6 years have not been established.

Single use for short-term sedation under medical supervision to facilitate EEG in children and adolescents from 1 to 18 years

Melatonin should be given 30 to 45 minutes before the anticipated start of the procedure as a single dose of 3 mg for children weighing less than 15 kg and 6 mg for those weighing more than 15 kg. Where possible this dose should be administered after a period of sleep deprivation to maximise the sedative effects. One further dose at 50% of the initial dose - 1.5 mg (<15 kg) or 3 mg (>15 kg) may be given if sleep is not achieved after 45 minutes. Therefore, the maximum daily dose is 4.5 mg in children weighing less than 15 kg and 9 mg for those weighing more than 15 kg.

Children under 1 year

The safety and efficacy of Melatonin in children aged below 1 year have not been established.

Other 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). However, individual elderly patients may be more likely to be slow metabolisers of melatonin with the potential for high residual morning levels of melatonin. In cases where there is excessive morning sleepiness, a lack of effect on DLMO and / or advancing sleep phase the possibility of impaired melatonin clearance, too high a dose, or too late a time of administration should be considered.

Renal impairment

There is only limited experience regarding the use of melatonin in patients with renal impairment. Caution should be exercised if melatonin is used by patients with renal impairment. Melatonin is not recommended for patients with severe renal impairment (see sections 4.4 and 5.2).

Hepatic impairment

There is no experience regarding the use of melatonin in patients with hepatic impairment. Limited data indicate that plasma clearance of melatonin is significantly reduced in patients with liver cirrhosis. Melatonin is not recommended in patients with hepatic impairment (see sections 4.4 and 5.2).

Genetic polymorphisms of CYP enzymes and other slow metabolisers

Polymorphisms in CYP1A2, CYP1A1 and CYP2C19 may affect first pass metabolism and systemic clearance of melatonin contributing to interindividual variability.

Method of administration

Melatonin is for oral use only.

Food can enhance the increase in plasma melatonin concentration (see section 5.2).

Intake of melatonin with carbohydrate-rich meals may impair blood glucose control for several hours (see section 4.4). It is recommended that food is not consumed 2 h before and 2 h after intake of melatonin.

A 5 ml graduated oral syringe with intermediate graduations of 0.1 ml and a “Press-In” Bottle Adaptor are provided with the product.

1. Open the bottle and at first use insert the “Press-In” Bottle Adaptor into the bottle neck

2. Insert the syringe into the adaptor.

3. Invert the bottle and draw out the required volume from the inverted bottle.

4. Return the bottle to the upright position and remove the filled syringe from the adaptor.

5. Slowly push the contents of the syringe into the mouth and swallow the medicine.

6. Replace the cap on the bottle (adaptor remains in place).

7. Rinse the syringe with water and allow to air-dry.

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

When treating insomnia in children and adolescents, melatonin should only be administered after other treatable causes of insomnia have been ruled out by appropriate specialist investigation and nonpharmacological measures have been inadequate.

Epilepsy

Melatonin has been reported to both increase and decrease seizure frequency in patients experiencing seizures (e.g. epileptic patients). Caution should be exercised when prescribing to patients with epilepsy and/or with multiple neurological defects and/or with concomitant medications that could increase seizure frequency.

Drowsiness

Melatonin may cause drowsiness. Melatonin should be used with caution if the effects of drowsiness are likely to be associated with a risk to patient safety. See section 4.7.

Impaired glucose tolerance and 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.

Auto-immune diseases

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

Renal and hepatic impairment

Only limited data are available on the safety and efficiency of melatonin in patients with renal impairment or hepatic impairment. Melatonin is not recommended for use in patients suffering from severe renal impairment or moderate or severe hepatic impairment.

Switching between formulations

Caution may be taken when switching between melatonin products as the mean Cmax on single dose administration for the suspension may be higher than that observed with tablet formulations.

Children and Adolescents

There is insufficient data to analyse the impact of long-term exposure to melatonin in children and adolescents on the sexual maturation of this population. There are theoretical risks based on biological effects of melatonin, e.g. immunological regulation, effects on the threshold for seizures and endocrinological effects, which could affect puberty development and fertility, respectively. Therefore, treatment should be taken for the shortest period and evaluated on a regular basis (at least every 6 months) to check that melatonin is still the most appropriate treatment.

Elderly (65 years old and over)

Exposure levels to melatonin after oral administration in young and moderately older adults are comparable. Although prolonged elevated levels of melatonin have been seen in some elderly patients it is unclear if all 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.

Excipients warnings

This medicinal product contains propylene glycol (E1520), methylparaben (E218), propylparaben (E216) and sodium.

This medicinal product contains 53 mg propylene glycol in each ml. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.

This medicinal product contains methylparaben (E218) and propylparaben (E216) which may cause allergic reactions (possibly delayed).

This medicinal product contains less than 1 mmol (23 mg) sodium per maximum 6 ml dose , 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.

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

- Caution is indicated in patients treated with fluvoxamine, since this agent increases melatonin levels (17-fold higher AUC and 12-fold higher serum C_{max}) by inhibiting its metabolism via CYP1A2 and CYP2C19. 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 CYP1A2.
- Caution should be exercised in patients receiving estrogen therapy (e.g. in the form of contraceptives or hormone replacement therapy), since estrogens

increase melatonin level by inhibiting its metabolism, primarily via inhibition of CYP1A2.

- CYP1A2 inhibitors (such as quinolones) may increase systemic melatonin levels.
- Caffeine, like melatonin, is metabolised by CYP1A2. Caffeine has been shown to increase serum concentrations of orally administered melatonin.

CYP1A2 inducers

- CYP1A2 inducers (such as carbamazepine and rifampicin) may reduce plasma concentrations of melatonin.
- Cigarette smoking may decrease melatonin levels due to induction of CYP1A2.

Pharmacodynamic interactions

Benzodiazepine-like hypnotics

Melatonin may enhance the sedative effect of benzodiazepines (e.g. midazolam, temazepam) and non-benzodiazepine hypnotics (e.g. zaleplon, zolpidem, zopiclone). In a study of jet lag therapy the combination of melatonin and zolpidem resulted in a higher incidence of morning sleepiness, nausea, and confusion, and reduced activity during the first hour after getting up, compared to zolpidem alone. The use of melatonin in combination with these drugs is not recommended.

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.

Warfarin

Melatonin may increase the anticoagulation activity of warfarin. The combination of warfarin or other vitamin K antagonists with melatonin may require dose adjustment of the anticoagulant drugs and should be avoided.

Alcohol

As alcohol can impair sleep and potentially worsen certain symptoms e.g. headache, morning fatigue, concentration it is recommended that alcohol is not consumed when taking melatonin.

Beta-blockers

Beta-blockers may suppress the endogenous melatonin but the clinical relevance of this is unknown when administering exogenous melatonin.

NSAIDs

Some NSAIDs, e.g. aspirin, ibuprofen, may reduce the endogenous secretion of melatonin, but the clinical relevance of this is unknown when administering exogenous melatonin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of melatonin in pregnant women. Exogenous melatonin readily crosses the human placenta.

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Melatonin is not recommended during pregnancy or in women of childbearing potential not using contraception.

Breast-feeding

There is insufficient information on the excretion of melatonin / metabolites in human milk. Endogenous melatonin is secreted in human milk.

Available pharmacodynamic/toxicological data in animals have shown excretion of melatonin / metabolites in milk (see section 5.3).

A risk to the suckling child cannot be excluded. Melatonin should not be used during breast-feeding.

Fertility

High doses of melatonin impaired male and female fertility in animals. The relevance of these data for human fertility is unknown.

Animal studies are insufficient with respect to effects on fertility (see section 5.3).

Melatonin is not recommended in women and men planning pregnancy.

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 melatonin is not recommended prior to driving and using machines.

4.8 Undesirable effects

Summary of the safety profile

After single doses of melatonin, nausea and vomiting were common adverse effects.

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.

Gastrointestinal symptoms, 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.

In longer term treatment of up to several months no additional long term adverse effects were seen, except an uncommon effect of abnormal dreams.

Tabulated list adverse reactions

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.

System Organ Class	**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)**	**Not known:** (cannot be established from the available data)
Infections and infestations				herpes zoster	
Blood and lymphatic system disorders				leucopenia, thrombocytopenia	
Immune system disorders					Hypersensitivity
Metabolism and nutrition disorders				Hypertriglyceridaemia, hypocalcemia, hyponatraemia	hyperglycaemia
Psychiatric disorders			irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmare, anxiety	mood altered, aggressive behaviour, agitation, stress disorientation, terminal insomnia, poor quality sleep, libido increased, depressed mood, depression	
Nervous system disorders		headache, somnolence	migraine, lethargy, psychomotor hyperactivity, dizziness	syncope (fainting), memory impairment, dreamy state, restless legs syndrome, disturbance in attention, 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, abdominal pain upper, dyspepsia, mouth ulceration, dry mouth, nausea	Gastroesophageal reflux disease, gastrointestinal disorder, diarrhoea, oral mucosal blistering, tongue ulceration, abdominal discomfort, vomiting, gastrointestinal sounds abnormal, flatulence, salivary hypersecretion, breath odour, gastrointestinal disorder, gastritis	Tongue oedema, mouth oedema
Hepatobilary			Hyperbilirubinae		

System Organ Class	**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)**	**Not known:** (cannot be established from the available data)
disorders			mia		
Skin and subcutaneous tissue disorders			Dermatitis, night sweats, pruritus, rash, dry skin	Eczema, erythema, hand dermatitis, psoriasis, rash pruritic, nail disorder	Angioedema,
Musculoskeletal and connective tissue disorders			Pain in extremity	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			Asthenia, chest pain, malaise	Fatigue, pain, thirst, crying,	Hypothermia
Investigations			Liver function test abnormal, weight increased	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 side effects did not differ significantly between children who received placebo and 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

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 Yellow Card Scheme.

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

Ingestion of daily doses of up to 300 mg 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 – 6600 mg) for several weeks.

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

Clearance of the active substance is expected within 12 hours of ingestion. Although prolonged residual systemic melatonin could be seen in slow metabolisers of melatonin.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Melatonin

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 around 02:00 – 04:00 hr 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- andMT3 receptors, as these receptors (particularly MT1 and MT2) are involved in the regulation of sleep (hypnotic effect) and circadian rhythms in general (chronobiotic effect).

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. Immediate release melatonin was assessed for its hypnotic effect on sleep onset or sedation, while the chronobiotic effect was assessed using timing of the endogenous dim light melatonin onset (DLMO) is a reliable and objective marker of circadian rhythm.

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 jet lag that are a consequence of such de-synchronisation.

The hypnotic effect of melatonin to improve sleep onset was most effective when given in the evening and followed the time course of plasma melatonin levels. The chronobiotic effect of melatonin, assessed using 0.5 mg and 3.0 mg phase response curves showed that exogenous melatonin produces the largest advance shifts when circulating endogenous levels are low - at least 1-2 hrs before DLMO, with phase shifts diminishing when endogenous melatonin increases, and high levels in the early morning potentially delaying the circadian clock.

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 (body clock) than to delay it, as required following westward travel. Clinical trials have found melatonin to reduce patient-assessed overall symptoms of jet lag by ~ 42%, 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% (Petrie 1989 et al. 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 effects 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 effects, plus nausea, are those typically associated with short-term use of melatonin in reviews of the safety of melatonin in humans.

Paediatric population with ADHD and sleep disorders

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

Delayed sleep wake phase disorder (DSWPD) in children, adolescents and young adults aged 6-25 years, where sleep hygiene measures have been insufficient.

The 4 pivotal studies included 308 subjects with an age range of 6-65 years. A clinically and statistically significant improvement in sleep onset times or sleep onset latency were reported in the melatonin treatment groups when compared to placebo

(Saxvig 2014, 25 minute improvement p=0.013; Sletten 2018, 44 minute improvement p<0.001; Van Geijlswijk 2010 a >30 min improvement, p<0.001; Van Maanen 2017a a 44 minute improvement p<0.01). Similar effects were seen for dim light melatonin onset (DLMO) a marker of circadian rhythmicity.

Single use for short-term sedation under medical supervision to facilitate electroencephalograms in children and adolescents.

In 3 clinical studies across 636 children up to 18 years of age, melatonin was effective in ensuring that the sleep EEG could be completed (Melatonin 89.4% versus Triclofos 91.2%, Lalwani 2021; Melatonin 73.3% versus Midazolam 36.7% Fallah 2014). An augmentation dose of melatonin was needed in up to 25.4% of patients.

5.2 Pharmacokinetic properties

Melatonin is a small, amphiphilic molecule (molecular weight 232 g/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 approximately 15%, owing to extensive first-pass metabolism (approximately 85%). Plasma T_{max} ranges between 30 and 45 minutes. A 3 mg dose of immediate-release melatonin raises plasma melatonin C_{max} to ~3400 pg/mL, which is ~60-times the nocturnal (endogenous) plasma melatonin C_{max} in young adults and ~170 times in older subjects, although both endogenous- and exogenous C_{max} show considerable inter-individual variation.

Data on the effect of intake of food at or around the time of intake of melatonin on its pharmacokinetics are limited, though suggest that concomitant food intake may increase bioavailability almost 2-fold. Food appears to have a limited effect on T_{max} for immediate-release melatonin. This is not expected to affect the efficacy or safety of melatonin, however, it is recommended that food is not consumed approximately 2 h before and 2 h after intake of melatonin.

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 that of their mother following ingestion of a 3 mg dose.

Biotransformation

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. A small proportion of patients appear to be slow metabolisers of melatonin. Polymorphisms in CYP1A2, CYP1A1 and CYP2C19 may affect first pass metabolism and systemic clearance of melatonin contributing to interindividual variability.

Elimination

Plasma elimination half-life ($T_{½}$) is ~ 45 minutes (normal range ~ 30 – 60 minutes) in healthy adults.

The half-life, on average, is comparable or slightly shorter in children compared to 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. These characteristics are consistent with a low risk of accumulation.

Linearity

Plasma melatonin C_{max} and AUC increase in a directly proportional, linear manner for oral doses of immediate-release melatonin in the range 1 – 10 mg , whereas Tmax and plasma $T_{½}$ remain constant.

Gender

Limited data suggest there is a potential of an increase in C_{max} for older women compared to men. A wide variability in C_{max} between different members of the same sex has also been observed. However, no pharmacodynamic differences between males and females were found despite differences in blood levels. Dose adjustment for women is not necessary.

Special populations

Elderly

Night-time endogenous melatonin plasma concentration is lower in the elderly compared to young adults. Limited data for plasma- T_{max}, C_{max}, elimination half- life ($T_{½}$), and AUC following ingestion of immediate-release melatonin do not indicate significant differences between younger adults and elderly persons in general, though the range of values (inter-individual variability) for each parameter tend to be greater in the elderly. Individual elderly patients may be more likely to be slow metabolisers of melatonin with the potential for high residual morning levels of melatonin.

Hepatic impairment

Limited data indicate that daytime endogenous blood melatonin concentration is markedly elevated in patients with liver cirrhosis, probably due to reduced clearance (metabolism) of melatonin. Serum $T_{½}$ 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.

Renal impairment

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.

Genetic polymorphisms of CYP enzymes and other slow metabolisers

Polymorphisms in CYP1A2, CYP1A1 and CYP2C19 may affect first pass metabolism and systemic clearance of melatonin contributing to interindividual variability. In cases where there is excessive morning sleepiness, a lack of effect on DLMO and / or advancing sleep phase the possibility of impaired melatonin clearance, too high a dose, or too late a time of administration should be considered.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, mutagenicity, genotoxicity and carcinogenic potential. Effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

After intra-peritoneal administration of a single, large dose of melatonin to pregnant mice, fetal body-weight and length tended to be lower, possibly due to maternal toxicity. Delay in sexual maturation in male and female offspring of the rat and ground squirrel occurred upon exposure to melatonin during pregnancy and post-partum. These data indicate that exogenous melatonin crosses the placenta and is secreted in milk, and that it may influence the ontogeny and activation of the hypothalamic-pituitary-gonadal axis. As the rat and ground squirrel are seasonal breeders, the implications of these findings for humans uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene Glycol (E1520)

Glycerol (E422)

Methylparaben (E218)

Propylparaben (E216)

Sucralose (E955)

Strawberry Flavour (including propylene glycol (E1520))

Sodium citrate

Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

Use within 2 month after first opening.

This medicinal product does not require any special storage conditions.

6.4 Special precautions for storage

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber, PET or glass bottle of 200 ml oral solution, safely closed with a HDPE child-resistant, tamper-evident screw cap with a LDPE liner. A LDPE, CE marked 5 ml graduated oral syringe with intermediate graduations of 0.1 ml and a LDPE, CE marked “press-in” syringe/bottle adaptor are also provided.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

SERB S.A.
Avenue Louise 480
1050 Brussels
Belgium

8 MARKETING AUTHORISATION NUMBER(S)

PL 43956/0018

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10 DATE OF REVISION OF THE TEXT

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