SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Melatonin 1 mg/ml oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml oral solution contains 1 mg melatonin.

Excipients with known effect

1 ml oral solution contains 1.6 mg sodium methyl parahydroxybenzoate, 150.5 mg propylene glycol,140 mg of sorbitol and less than 1.0 mg of ethanol (less than 5.0 mg of ethanol at maximum dose).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

Colourless to slightly yellowish, opalescent solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Melatonin 1 mg/ml oral solution is indicated for:

- Short-term treatment of jet-lag in adults (refer to section 5.1).
- 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

Jet-lag in adults

The recommended dose is 2 mg (2 ml) daily for a maximum of 5 days. The dose may be increased to 5 mg (5 ml) daily if the initial 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 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 1 mg/ml oral solution should not be taken before 20:00 hr or after 04:00 hr at destination.

Melatonin 1 mg/ml oral solution may be taken for a maximum of 16 treatment periods per year.

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.

Recommended starting dose is 1-2 mg (1-2 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 limited data 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 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 1 mg/ml oral solution 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.

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

Special populations

Elderly

Caution should be exercised in the elderly population due to greater variability in plasma melatonin concentrations in this age group and potential for morning drowsiness. Elderly patients should be commenced on a low dose, with cautious dose increase or reduction as necessary (see section 5.2).

Renal impairment

There is only limited experience of administered melatonin in patients with renal impairment. Caution should be exercised if melatonin is used by patients with renal impairment. Melatonin 1 mg/ml oral solution is not recommended for patients with severe renal impairment (see section 5.2).

Hepatic impairment

There is no experience regarding the use of administered melatonin in patients with hepatic impairment. Limited data indicate markedly elevated endogenous melatonin levels in patients with liver cirrhosis. Melatonin 1 mg/ml oral solution is not recommended in patients with moderate or severe hepatic impairment (see section 5.2).

Paediatric population (under 6 years of age)

Melatonin 1 mg/ml oral solution is not recommended for use in children under 6 years of age.

Method of administration

Oral use. A 5 ml syringe with 0.1ml graduation and a syringe adaptor are provided with the product.

How to use the medicine:

1) Make sure the cap is firmly closed before you shake the bottle.
2) Open the cap by pressing down and turn anti-clockwise.
3) At first use, insert the adaptor into the neck of the bottle, by keeping the bottle on a flat surface and the adaptor's flat surface facing up and pressing it down. The adaptor must after this always be kept in the bottle.
4) Make sure the plunger is fully down in the syringe before your insert the syringe into the adaptor.
5) Invert the bottle upside down and slowly pull the plunger down fully so that the syringe fills with medicine. Push the plunger back up completely to expel any large air bubbles that may be trapped inside the oral syringe. Then pull the plunger slowly back to the volume you need for your dose.

6) Turn the whole bottle with the syringe still included the right way up before you take the syringe out of the bottle.
7) Sit upright and discharge the syringe content slowly into the mouth and swallow the medicine.
8) Rinse the syringe and replace the cap on the bottle (the adaptor remains in the bottle).

Melatonin may act more quickly when administered as an oral solution compared with tablet or capsule formulations. Care should be exercised when switching between tablet or capsule and solution formulations.

Food may increase the absorption of melatonin, leading to higher plasma melatonin concentration (see section 5.2). It is recommended that food is avoided for 2 h before and 2 h after taking Melatonin 1 mg/ml oral solution.

Melatonin taken in close proximity to carbohydrate-rich meals may also impair blood glucose control for several hours (see section 4.4). In patients with diabetes or impaired glucose tolerance, melatonin should ideally be taken at least 3 hours after a meal.

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 1 mg/ml oral solution.

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

Elderly

Caution should be exercised in treatment of the elderly due to the potential for greater variability in plasma levels and of sensitivity to the effects of melatonin in this age group. Cautious dose titration is therefore recommended in the elderly.

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.

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 1 mg/ml oral solution is not recommended in patients with autoimmune diseases.

Drowsiness

Melatonin can cause drowsiness. Melatonin 1 mg/ml oral solution should be used with caution if the effects of drowsiness are likely to be associated with a risk to patient safety.

Food interaction

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.

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 1 mg/ml oral solution is not recommended for use in patients suffering from severe renal impairment or moderate or severe hepatic impairment.

Warfarin

Due to the potential for pharmacokinetic interaction between warfarin and melatonin, there is a risk of increased anti-coagulation effect, with bleeding, if melatonin is taken alongside warfarin (see section 4.5) The patient should be closely monitored or switched to an alternative anti-coagulant, during melatonin use.

Switching between formulations

Caution may be taken when switching between melatonin products.

Paediatric population (under 6 years of age)

Melatonin 1 mg/ml oral solution is not recommended for use in children younger than 6 years of age.

This medicinal product contains sodium

Melatonin 1mg/ml oral solution contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially ‘sodium- free’.

This medicinal product contains sodium methyl parahydroxybenzoate

May cause allergic reactions (possibly delayed).

This medicinal product contains propylene glycol

Melatonin 1mg/ml oral solution contains 150.5 mg propylene glycol in each ml.

This medicinal product contains sorbitol.

Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

This medicinal product contains ethanol.

Melatonin 1mg/ml oral solution contains less than 1.0 mg of alcohol (ethanol) in each ml. The amount in 1 ml of this medicine is equivalent to less than 0.03 ml beer or 0.01 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

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

- 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.
- Caution is indicated in patients treated with fluvoxamine, since this agent increases melatonin levels (17-fold higher AUC and 12-fold higher serum Cmax) 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 CYP2D.

- 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.
- CYP1A2 inducers (such as carbamazepine and rifampicin) may reduce plasma concentrations of melatonin.
- Cigarette smoking may decrease melatonin levels due to induction of CYP1A2.
- 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}).
- Melatonin may increase the anticoagulation activity of warfarin due to metabolism by CYP2C19, CYP1A and CYP2C9 families (see section 4.4).

Pharmacodynamic interactions

- 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.
- Melatonin may reduce the hypotensive effect of nifedipine, so caution should be exercised in this combination and dose adjustment of nifedipine may be needed.
- Alcohol should not be taken with melatonin as it may reduce the effect of melatonin on sleep.

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 1 mg/ml oral solution 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. Available pharmacodynamic / toxicological data in animals have shown excretion of melatonin / metabolites milk (see section 5.3). A risk for the breastfed child cannot be excluded. Melatonin should not be used during breast-feeding.

Fertility

There is limited clinical data about effects of melatonin on fertility. High doses of melatonin and use for longer periods than indicated may compromise fertility in humans. Animal studies are insufficient with respect to effects on fertility.

Melatonin 1mg/ml oral solution is not recommended in women and men planning pregnancy.

4.7 Effects on ability to drive and use machines

Melatonin has moderate effect on the ability to drive and use machines. Melatonin may cause drowsiness and may decrease alertness for several hours, therefore use of Melatonin 1mg/ml oral solution is not recommended prior to driving and using machines.

4.8 Undesirable effects

Summary of the safety profile

Melatonin causes few and no serious adverse reactions in the short term, up to three months.

Drowsiness/sleepiness, headache, and dizziness/disorientation are the most frequently report 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.

Tabulated risks of adverse reactions

In the table below all adverse reactions are listed according to organ class and frequency. Frequencies are defined as: Very common (≥1/10); Common (≥100 to <1/10); Uncommon (≥1/1000 to <1/100); Rare (≥1/10 000 to <1/1000); Very rare (<1/10000); Not known (cannot be estimated from the available data). Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

System Organ Class	**Frequency**	**Adverse Events**
Infections and infestations	Rare	Herpes Zoster
Blood and lymphatic system	Rare	Leukopenia, thrombocytopenia

disorders		
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, stress symptoms, disorientation, early morning awakening, libido increased, depressed mood, depression
Nervous system disorders	Common	Headache, somnolence
	Uncommon	Migraine, lethargy, psychomotor hyperactivity, dizziness
	Rare	Syncope (fainting), memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, paraesthesia
	Not known	Drowsiness, sedation
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 flushes
Gastrointestinal disorders	Uncommon	Abdominal pain, abdominal pain upper, dyspepsia, oral ulcers, dry mouth, nausea
	Rare	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	Uncommon	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis, night sweats, pruritus, rash, pruritus generalised, dry skin
	Rare	Eczema, erythema, hand dermatitis, psoriasis, rash generalised, rash pruritic, nail disorder
	Not known	Angioedema, oedema of mouth, tongue oedema
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
	Not known	Galactorrhea
General disorders and administration site conditions	Uncommon	Malaise, chest pain
	Rare	Fatigue, pain, thirst
Investigations	Uncommon	Liver function test abnormal, weight increased
	Rare	Hepatic enzyme increased, blood electrolytes abnormal, laboratory test abnormal

Pediatric 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 at 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.

Due to the short half-life of melatonin, complete elimination of melatonin from the body is expected within 12 hours of ingestion.

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: Hypnotics and sedatives, melatonin receptor agonists

ATC code: N05CH01.

Melatonin is a hormone secreted by the pineal gland, 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- and MT3 receptors, as these receptors (particularly MT1 and MT2) are involved in the regulation of sleep and circadian rhythms in general.

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 jet-lag that are a consequence of such desynchronisation.

Clinical efficacy and safety

Jet-lag in adults

Melatonin 1 mg/ml oral solution is recommended to adult travelers flying across ≥5 time zones, particularly in an easterly direction, and especially if they have experienced jet-lag symptoms on previous journeys. Travelers crossing 2-4 time zones can also use it if needed.

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 ~44%, and to shorten the duration of jet-lag. In 2 studies of flights over 12 time-zones melatonin effectively reduced the duration of jet-lag by ~33%. Due to the potential for incorrectly timed intake of melatonin to have no effect, or to cause an adverse effect, on resynchronisation 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 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.

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

Clinical studies demonstrated the effectiveness and safety of melatonin at doses of 1-6 mg before bedtime to phase shift the circadian system and improve sleep disturbances of paediatric patients with ADHD, by decreasing sleep latency and increasing the total sleep time.

Clinical studies, including paediatric (aged 6-14 years) patients with ADHD also suffering from chronic sleep-onset insomnia who were administered melatonin at initial doses ranging from 3 to 6 mg, within a few hours prior to a scheduled bedtime, have shown improvements in sleep onset (about 0.5-2 h), sleep duration (approximately 0.33-1 h) and sleep latency (~20 min), while adverse reactions reported were infrequent and mild, e.g., transient headaches and dizziness.

<u>Paediatric population</u>

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 (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. 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. 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 ~ 15%, owing to first-pass metabolism of ~ 85%. Plasma T_{max} is ~ 50 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}, though 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 1 mg/ml oral solution, 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 and is only slightly lower (~ 15 – 35%) than 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.

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. Dosage once daily in combination with the short half-life means minimal accumulation of melatonin during regular treatment. 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.

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 – 6 mg whereas T_{max} and plasma $T_{½}$ remain constant.

Gender

Limited data suggest that C_{max} and AUC following ingestion of immediate-release melatonin may be higher (potentially roughly double) in women compared to men, however a large variability in the pharmacokinetics is observed. Plasma melatonin half-life does not appear to be significantly different in men and women.

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.

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

Literature data indicate that there is no accumulation of melatonin after repeated dosing (3 mg for 5 – 11 weeks) in patients on stable haemodialysis. However, 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.

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

- Sodium methyl parahydroxybenzoate (E 219)
- Sorbitol, liquid (non-crystallising) (E 420)
- Propylene glycol (E 1520)

- Xanthan gum
- Citric acid
- Orange flavour [ethanol, acetaldehyde, limonene, linalool]
- Sodium citrate
- Saccharin sodium
- Water, purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

Melatonin 1mg/ml oral solution should not be used longer than 5 months after first opening.

6.4 Special precautions for storage

Do not store above 30°C.

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

6.5 Nature and contents of container

Melatonin 1mg/ml oral solution is available in:
Amber (type III) glass bottle of 100 ml or 150 ml of oral solution, sealed with a child-resistant and tamper evident HDPE cap, with LDPE syringe adaptor and LDPE dosimetric syringe of 5ml (with 0.1ml graduation).

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

Glenmark Pharmaceuticals Europe Ltd,

Laxmi House, 2-B Draycott Avenue, Kenton, Harrow, Middlesex, HA3 0BU,

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 25258/0402

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/10/2025

10 DATE OF REVISION OF THE TEXT

23/03/2026