SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ceyesto 1 mg/ml Oral Solution
Melatonin ALTURiX 1 mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 1 mg of melatonin.

Excipient(s) with known effect:
Propylene glycol: 52 mg per 1 ml dose
Benzyl alcohol: 6 mg per 1 ml dose

Each 1 ml of oral solution contains 1 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

Colourless to yellowish transparent liquid with strawberry odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceyesto / Melatonin ALTURiX 1 mg/ml Oral Solution is indicated for:

(i) 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.

(ii) Short-term treatment of jet lag in adults.

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

(iv) 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

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 a day, 1-2 hours before the fixed desired bedtime, given as 1-2 ml of the oral solution. The dose of melatonin should be adjusted individually 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.

After 6 weeks of treatment, the physician should evaluate the treatment effect and consider stopping 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.

Short-term treatment of jet lag in adults:
The standard dose is 3 mg daily, taken as 3 ml of the oral solution for a maximum of 5 days. If the standard dose does not adequately alleviate symptoms, the dose may be increased to 6 mg, taken as 6 ml of the oral solution. 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 in the time zone. Due to the potential for incorrectly timed intake of melatonin to have no

effect, or an adverse effect, on resynchronization following jet-lag, this medicinal product should not be taken before 20:00 hr or after 04:00 hr at destination.

This medicinal product may be taken for a maximum of 16 treatment periods per year.

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, 30-60 minutes before bedtime.

The dose of melatonin should be adjusted individually 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.

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 at least 3 months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen.

The patient should be monitored at regular intervals (at least every 6 months) to check that melatonin is still the most appropriate treatment.

During ongoing treatment discontinuation attempts should be attempted regularly, e.g. once per year and treatment discontinued if it is not effective.

If the sleep disorder has started during treatment with other medicinal products, dose adjustment or switching to another product should be considered. If significant problems are seen in sleep maintenance or early morning waking, an alternative formulation of melatonin should be considered.

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

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.

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 30-45 minutes before the anticipated start of the procedure as a single dose of 3mg 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.

Due to the presence of benzyl alcohol in the formulation and the risk of accumulation especially in younger children it is not recommended to perform more than one melatonin assisted EEG in each 24 hour period.

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.

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.

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

Hepatic impairment
There is only limited experience regarding the use of this medicinal product in patients with hepatic impairment. Limited data indicate that plasma clearance of melatonin is significantly reduced in patients with liver cirrhosis. This medicinal product is not recommended in patients with moderate or severe hepatic impairment (see Sections 4.4 and 5.2).

Method of administration
This medicinal product is for oral use only. A plastic 5 ml oral syringe (graduated every 0.5 ml from 0.5 to 5 ml) is provided with the product.

1. Open the bottle; on first opening the seal is broken.
2. Check the syringe adaptor is already securely in place.
3. Insert the oral syringe firmly into the adaptor and turn the bottle upside down. This will allow you to fill the syringe with the dose that needs to be administered.
4. Holding the bottle, slowly draw out the plunger until you reach the marking for the prescribed dose.
5. Turn the bottle up the correct way and carefully take the syringe out of the bottle.
6. The patient should sit upright when taking the medicine. Place the tip of the syringe in the patient’s mouth and slowly push the plunger down to release the dose.
7. Repeat steps 3-6 if doses greater than 5 ml are required.
8. Rinse the syringe with water after each use and replace the cap on the bottle.

If necessary, this medicinal product can be administered via a silicone gastric, duodenal or nasal feeding tube (see section 6.6). Rinse the tube twice with at least 10 ml of water following administration.

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 hours before and 2 hours after intake of this medicinal product.

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

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

Melatonin has been reported to increase, decrease and have no effect on seizure frequency. Because of the uncertainty of the effect of melatonin on epileptic seizures, some caution should be exercised for use in people with epilepsy.

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

Limited data suggest that melatonin taken in close proximity to ingestion of carbohydrate-rich meals may impair blood glucose control for several hours. This medicinal product should be taken at least 2 hours before and at least 2 hours after a meal; ideally at least 3 hours after meals by persons with significantly impaired glucose tolerance or diabetes.

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

<u>Children and Adolescents</u>
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 the treatment of this age group and individual dosage is recommended.

Excipient warnings
This medicinal product contains 6mg / ml of benzyl alcohol.

Benzyl alcohol may cause allergic reactions and has been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in young children. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Benzyl alcohol containing products should not be used in pre-term or full-term neonates (up to 4 weeks) unless strictly necessary.

Large amounts of benzyl alcohol can build-up in the body and may cause side effects (metabolic acidosis). Large volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment or those that are pregnant or breast-feeding. Caution is also advised in young children (< 3 years) due to the risk of accumulation.

This medicinal product contains 52mg / ml of propylene glycol. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

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 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 advised 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.
- 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

- Melatonin may enhance the sedative effect of benzodiazepines (e.g. midazolam, temazepam) and non-benzodiazepine hypnotics (e.g. 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 affect the anticoagulation activity of warfarin.
- 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 this medicinal product.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of melatonin in pregnant women.

Exogenous melatonin readily crosses the human placenta.

Animal studies are insufficient with respect to embryofoetal development (see section 5.3).

This medicinal product is not recommended during pregnancy or in women of childbearing potential not using contraception.

Breast-feeding

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 in milk (see 5.3).

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

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 (see Section 5.3).

This medicinal product 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 this medicinal product is not recommended immediately before 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.

Gastrointestinal symptoms, drowsiness, headache and dizziness are also 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 additonal 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)	Uncommen (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not Known: Cannot be established from the available data
Blood and lymphatic system disorders				Leucopenia, thrombocytope-nia	
Immune system disorders					Hypersensitivity reaction
Metabolism and nutrition disorders				Hypertriglycerid-aemia	Hyperglycaemia
Psychiatric disorders			Irritability, nervousness, restlessness, abnormal dreams, anxiety	Mood altered, aggressive behaviour, disorientation, libido increased	
Nervous system disorders		Headache, somnolence	Dizziness	Syncope (fainting), memory	

				impairment, restless legs syndrome, paraesthesia	
Eye disorders				Visual acuity reduced, vision blurred, lacrimation increased	
Ear and labyrinth disorders				Vertigo positional, vertigo	
Cardiac disorders				Palpitations	
Vascular disorders			Hypertension	Hot flushes	
Gastrointestinal disorders			Abdominal pain, upper abdominal pain, dyspepsia, oral ulcers, dry mouth, nausea	Vomiting, flatulence, salivary hypersecretion, halitosis, gastritis	
Skin and subcutaneous tissue disorders			Pruritus, rash, dry skin	Nail disorder	Tongue edema, edema of the oral mucosa
Musculoskeletal and connective tissue disorders				Arthritis, muscle spasms	
Renal and urinary disorders			Glycosuria, proteinuria	Polyuria, haematuria	
Reproductive system and breast disorders				Priapism, prostatitis	Galactorrhoea
General disorders and administration site conditions			Chest pain, malaise	Thirst	
Laboratory and other examinations			Liver function test abnormal, weight increased	Blood electrolytes abnormal	

Paediatric population

A low frequency of in general mild adverse reactions have been reported in the paediatric population. 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 when high quality synthetic melatonin was given together with the currently recommended posology.

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- and MT3 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 through its chronobiotic effect. 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) as a reliable and objective marker of circadian rhythm.

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

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.

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% (Petrie 1989, Cardinali 2002). 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.

Insomnia in children and adolescents aged 6-17 years with attention deficit hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient.
Melatonin advanced sleep onset 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 (van der Heijden 2007). 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.

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.

Safety in all indications
Adverse effects associated with melatonin use in clinical studies involving melatonin doses of 0.5 to 12 mg were typically mild. Transient drowsiness / sedation, headache, dizziness / disorientation and gastrointestinal disorders were the most common 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.

The inter-individual variability has been estimated to be 50-70 % and the intra-variability at ~30-50%. The individual differences in absorption, distribution, metabolism and elimination between subjects potentially play a role in the variability reported.

<u>Absorption</u>

Orally administered melatonin is almost completely absorbed. Oral bioavailability is ~15%, owing to first-pass metabolism of ~85%. Plasma T_{max} is between 15 and 60 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} and AUC show extensive inter-individual variability of 50-70 % and intra-individual variability of 30-50%, with external and intrinsic factors contributing to differences in circadian rhythm, absorption, distribution, metabolism and elimination between and within subjects.

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 this medicinal product however, it is recommended that food is not consumed approximately 2 hours before and 2 hours 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 organs, 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 with maximum levels reached at between 1 and 6 hours with a median of 120 minutes returning to baseline at 24 hours. 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 (T½) is ~45 minutes (normal range ~30 – 120 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. 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 3 – 6 mg whereas T_{max} and

plasma T½ remain constant. Dose linearity was demonstrated between 1 mg and 12 mg.

Special populations

Older people
Limited data for plasma-T_{max}, C_{max}, elimination half-life (T½), 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 (interindividual 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.

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.

Hepatic impairment
As the liver is the primary site of melatonin metabolism, hepatic impairment can be expected to result in increased exposure to melatonin. Limited data indicate that blood melatonin concentrations were elevated in patients with liver cirrhosis and serum T½ was double that of controls.

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 to increase in patients with more advanced renal impairment.

Patients with comorbid medical conditions including psychiatric disorders
Optimal management of these conditions often improves sleep; however, insomnia may persist even with resolution of the medical condition or with partial, but maximal, medical management. As bidirectional relationships exist among many medical conditions and insomnia, addressing insomnia may improve both the patient's medical status and their quality of life. Consideration should be given to managing insomnia in certain patients where clinically appropriate.

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, carcinogenic potential.

Effects were observed only at exposures considered sufficiently in excess of the maximum human exposure.

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. The implications of these findings for humans is uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucralose (E 955)

Benzyl alcohol

Sodium ascorbate

Propylene glycol (E 1520)

Strawberry flavour (including propylene glycol (E 1520))

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

After first opening store below 25°C and use within 1 month.

6.4 Special precautions for storage

Store below 25°C.
Keep the bottle in the outer carton in order to protect from light.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber, type III glass bottle of 100 ml, 150 ml or 200 ml nominal capacity, closed with a white polypropylene (PP) / polyethylene (PE), child-resistant and tamper-evident screw cap with a PE syringe adaptor insert.

A plastic 5 ml oral syringe (graduated from 0.5 to 5 ml in 0.5 ml increments) is provided.

6.6 Special precautions for disposal

Disposal
No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Feeding tubes
This medicinal product is compatible with silicone feeding tubes. The use of tubes made of polyurethane is not recommended as compatibility has not been demonstrated.

To flush the feeding tube, rinse twice with at least 10ml of water following administration.

7 MARKETING AUTHORISATION HOLDER

ALTURiX Ltd
287 Upper Fourth Street
Milton Keynes
MK9 1EH
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 44490/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/09/2023

10 DATE OF REVISION OF THE TEXT

09/01/2024