SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ceyesto 3 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 3 mg melatonin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, round, convex tablet with logo 7, diameter 7 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ceyesto is indicated for:

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

4.2 Posology and method of administration

Posology

Jet-lag in adults:

The standard dose is one 3 mg tablet daily at local time to go to bed starting on arrival at destination for a maximum of 4 days. Other dosages from other manufacturers are available to achieve higher than 3 mg dose if required.

The dose that adequately alleviates symptoms should be taken for the shortest period. Due to the potential for incorrectly timed intake of melatonin to have no effect, or to cause 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.

Paediatric population
The safety and efficacy of melatonin in children and adolescents less than 18 years in jet lag has not been established.

Insomnia in children and adolescents aged 6-17 years with ADHD:
Melatonin 3 mg dose is taken 30-60 minutes before bedtime. Ceyesto is suitable only when the lowest effective dose has been established to be 3 mg. Maximum dose: 3 mg.

Limited data are available for up to 3 months of treatment. The physician should evaluate the treatment effect at regular intervals and consider stopping treatment if no clinically relevant treatment effect is seen.

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

Children below 6 years of age
Ceyesto tablets are not recommended for children below 6 years with ADHD. The safety and efficacy of melatonin in children less than 6 years has not been established.

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

Renal impairment
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 cirrhosis. Melatonin is not recommended for patients with hepatic impairment (see sections 4.4 and 5.2).

Method of administration
Oral use. Tablets should be swallowed with a glass of water. Intake of food at or around the time of intake of melatonin is not expected to affect the efficacy or safety of melatonin, however, it is recommended that food is not consumed approximately 2 h before or 2 h after intake of melatonin (see section 5.2).

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

Seizures
Melatonin may increase seizure frequency in patients experiencing seizures (e.g. epileptic patients). Patients suffering from seizures must be informed about this possibility before using Melatonin 3 mg film-coated tablets.

Melatonin may promote or increase the incidence of seizures in children and adolescents with multiple neurological defects.

Drowsiness
Melatonin may cause drowsiness. Therefore the product should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety (see section 4.7).

Autoimmune diseases
No clinical data exist concerning the use of melatonin in individuals with autoimmune diseases. Therefore, melatonin is not recommended for use in patients with autoimmune diseases.

Hepatic and renal impairment
There is only limited experience of safety and efficacy regarding the use of melatonin in patients with hepatic or renal impairment. Melatonin is not recommended for patients with hepatic impairment or severe renal impairment (see sections 4.2 and 5.2).

Cardiovascular conditions
There is limited data that melatonin may cause adverse effects on blood pressure and heart rate in populations with cardiovascular conditions and concurrent antihypertensive medications. It is unclear whether these adverse effects are attributable to melatonin itself or to melatonin-drug interactions. Melatonin is not recommended for use in patients with cardiovascular conditions and concurrent antihypertensive medication.

Concomitant use of anticoagulants
Caution is advised when using melatonin together with anticoagulant drugs, including warfarin and novel direct-acting anticoagulants, as melatonin may enhance the effect of these drugs resulting in increased risk of bleeding (see section 4.5).

Children and adolescents
Currently the safety profile of melatonin in children and adolescents is not fully established, especially in long-term use. Long-term melatonin use may negatively affect blood glucose control, pubertal development and sexual maturation.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Pharmacokinetic interactions

- Melatonin's metabolism is mainly mediated by CYP1A enzymes. Therefore, interactions between melatonin and other active substances as a consequence of their effect on CYP 1A enzymes are possible.
- Caution should be exercised in patients on fluvoxamine, which increases melatonin levels (by 17-fold higher AUC and 12-fold higher serum C_{max}) by inhibiting its metabolism by hepatic cytochrome P450 (CYP) isozymes CYP1A2 and CYP2C19. The combination should be avoided.
- Caution should be exercised in patients on 5- or 8-methoxypsoralen (5 and 8-MOP), which increases melatonin levels by inhibiting its metabolism.
- Cigarette smoking may decrease melatonin levels due to induction of CYP 1A2.
- Caution is advised in patients taking cimetidine, since this agent increases plasma melatonin levels by inhibiting its metabolism by CYP1A2.
- Caffeine increases the concentrations of both endogenous and orally administered melatonin by inhibiting CYP1A2 catalysed melatonin metabolism.
- Caution should be exercised in patients on oestrogens (e.g. contraceptive or hormone replacement therapy), which increase melatonin levels by inhibiting its metabolism by CYP1A1 and CYP1A2.
- CYP1A2 inhibitors such as quinolones may give rise to increased melatonin exposure.
- CYP1A2 inducers such as carbamazepine and rifampicin may reduce plasma concentrations of melatonin.
- There is a large amount of data in the literature regarding the effect of adrenergic agonists/antagonists, opiate agonists/antagonists, antidepressant medical products, prostaglandin inhibitors, benzodiazepines, tryptophan and alcohol, on endogenous melatonin secretion. Whether or not these active substances interfere with dynamic or kinetic effects of melatonin or vice versa has not been studied.

Pharmacodynamic interactions

- Alcohol should not be taken with melatonin, because it reduces the effectiveness of melatonin on sleep. Alcohol can impair sleep and potentially worsen certain symptoms of jet-lag (e.g. headache, morning fatigue, impaired concentration).
- Melatonin may enhance the sedative properties of benzodiazepines and non-benzodiazepine hypnotics, such as zaleplon, zolpidem and zopiclone. In a clinical trial, there has been clear evidence for a transitory pharmacodynamic interaction between melatonin and zolpidem one hour following co-dosing. Concomitant administration resulted in increased impairment of attention, memory and co-ordination compared to zolpidem alone.
- Melatonin has been co-administered in studies with thioridazine and imipramine, active substances with affect the central nervous system. No

clinical significant pharmacokinetic interactions were found in each case. However, melatonin co-administration resulted in increased feelings of tranquillity and difficulty in performing tasks compared to imipramine alone, and increased feelings of “muzzy-headedness” compared to thioridazine alone.

- Caution is advised in patients taking nifedipine, since concurrent use of melatonin and nifedipine may increase blood pressure. Concomitant use of melatonin and warfarin may lead to enhanced anticoagulation – INR should be checked when used together. Melatonin may also enhance the effect of direct-acting anticoagulants (e.g. dabigatran, rivaroxaban, apixaban, edoxaban).

4.6 Fertility, pregnancy and lactation

Pregnancy

For melatonin, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, partitution or postnatal development (see section 5.3). Exogenous melatonin readily crosses the human placenta. In view of lack of clinical data, use in pregnant women and by women intending to become pregnant is not recommended.

Breastfeeding

Endogenous melatonin was measured in human breast milk thus exogenous melatonin is probably secreted into human milk. There are data in animal models including rodents, sheep, bovine and primates that indicate maternal transfer of melatonin to the foetus via the placenta or in the milk. Therefore, melatonin should not be used during breast-feeding.

Fertility

There is no data about possible adverse effects of short-term use of melatonin on human fertility.

4.7 Effects on ability to drive and use machines

Ceyesto has moderate influence on the ability to drive and use machines. Melatonin may cause drowsiness and impair alertness for hours; therefore the product should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety.

4.8 Undesirable effects

Summary of the safety profile

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

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 reaction
Metabolism and nutrition disorders				hypertriglyceridaemia, hypocalcaemia, hyponatremia	
Psychiatric disorders			irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety	mood changes, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, increased libido, depressed mood, depression	

Nervous system disorders			migraine, headache**,** lethargy, psychomotor hyperactivity, dizziness**,** somnolence	syncope, impaired memory, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, paraesthesia	
Eye disorders				acuity reduced, vision blurred, increased lacrimation	
Ear and labyrinth disorders				positional vertigo, vertigo	
Cardiac disorders				angina pectoris, palpitations	
Vascular disorders			hypertension	hot flushes	
Gastrointestinal disorders			abdominal pain, abdominal pain upper, dyspepsia, mouth ulceration, dry mouth, nausea	gastro-oesophageal 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			hyperbiliru-binaemia		
Skin and subcutaneous tissue disorders			dermatitis, night sweats, pruritus, rash, pruritus generalised, dry skin	eczema, erythema, hand dermatitis, psoriasis, generalised rash, pruritic rash, nail disorder	angioedema, oedema of mouth, tongue oedema

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	fatigue, pain, thirst	
Investigations			liver function test abnormal, weight increased	hepatic enzyme increased, blood electrolytes abnormal, laboratory test abnormal	

Paediatric population
A low frequency of in general mild adverse reactions have been reported in the literature and paediatric population in short-term use (up to 4 weeks). The number of adverse reactions has not differed significantly between children who have received placebo compared to melatonin. The most common adverse reactions were headache, hyperactivity, dizziness and abdominal pain. No serious adverse reactions have been observed. Long term effects are poorly studied (see section 5.1).

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

Administration of daily doses of up to 300 mg of melatonin without causing clinicaly significant adverse reaction have been reported in the literature.

If overdose occurs, drowsiness is to be expected. Clearance of the active substance is expected within 12 hours after ingestion. No special treatment is required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin. Physiologically, melatonin secretion increases soon after the onset of darkness, peaks at 2-4 am and diminishes during the second half of the night. Melatonin is associated with the control of circadian rhythms and entrainment to the light-dark cycle. It is also associated with a hypnotic effect and increased propensity for sleep. Melatonin administered earlier or later than the nocturnal peak in melatonin secretion can, respectively, advance or delay the circadian rhythmicity of melatonin secretion.

Mechanism of action
The activity of melatonin at the MT1, MT2 and MT3 receptors is believed to contribute to its sleep-promoting properties, as these receptors (mainly MT1 and MT2) are involved in the regulation of circadian rhythms and sleep regulation.

Clinical efficacy and safety
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.

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.

Paediatric population
The safety and efficacy of melatonin in children and adolescents aged 0 – 18 years in the short-term treatment of jet-lag have not been established.

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 6mg 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.

There is very little long-term safety data on immediate-release melatonin products specifically in children and adolescents with ADHD.

5.2 Pharmacokinetic properties

Absorption

The absorption of orally ingested melatonin is complete in adults.

Bioavailability is in the order of 15%. There is a signifigant first pass effect with an estimated first pass metabolism of 80-90%. The T_{max} occurs usually approximately 50 minutes (normal range 15 to 90 minutes) after administration.

Data on the effect of intake of food at or around the time of intake of melatonin are limited. Food appears to have negligible effect on T_{max} for immediate-release melatonin, but to greatly increase variability in Cmax. The latter is not expected to affect the efficacy or safety of melatonin, however, it is recommended that food is not consumed approximately 2 h before or 2 h after intake of melatonin.

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.

Distribution

The *in vitro* plasma protein binding of melatonin is approximately 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.

Biotransformation

Melatonin is mainly metabolised by the liver. Experimental data suggest that the cytochrome P450 isoenzyme system's CYP1A1 and CYP1A2 are primarily responsible for melatonin metabolism, with CYP2C19 of minor importance. The principal metabolite is the inactive 6-sulphatoxy-melatonin. Metabolism is very rapid, metabolite level rising within minutes.

Elimination

Metabolites are excreted renally, 80% as 6-sulphatoxy-melatonin.

The elimination half life (t½) is approximately 45 minutes.

There are large differences in the pharmacokinetics of melatonin between individuals.

Linearity

The kinetics of oral melatonin are linear over range 1-8 mg.

Gender

Limited data suggest that Cmax and AUC following ingestion of immediate-release melatonin may be higher (potentially roughly double) in women compared to men, but also that the difference between the sexes is less than variation amongst members of the same sex, particularly women in whom Cmax appears to vary multiplefold. Plasma half-life does not appear to be significantly different in men and women.

Special populations

Elderly

Metabolism of melatonin decreases with age. Night-time endogenous melatonin plasma concentration is lower in the elderly compared to young adults. Limited data for plasma/serum Tmax, Cmax, 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 (inter-individual variability) for each parameter (particularly Tmax and AUC) tend to be greater in the elderly.

Renal impairment

Published data indicate that there is no accumulation of melatonin after repeated dosing in patients on stable haemodialysis. As melatonin is primarily excreted as metabolites in the urine, serum/plasma levels of melatonin metabolites can be expected increase in patients with more advanced renal impairment.

Hepatic impairment

Limited data indicate that daytime endogenous serum/plasma melatonin concentration is markedly elevated in patients with cirrhosis, probably due to reduced clearance of melatonin; serum T½ in cirrhosis patients was double that of controls in study. As the liver is the primary site of melatonin metabolism, hepatic impairment can be expected to result in increased exposure to exogenous melatonin.

5.3 Preclinical safety data

Non-clinical data 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

Calcium hydrogen phosphate dihydrate
Microcrystalline cellulose
Magnesium stearate
Silica colloidal anhydrous
Starch pregelatinised

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister pack: 3 years

Tablet container: 4 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

10, 30 and 50 tablets in blister packs (PVC/Al).
10, 30 and 50 tablets in tablet container (container HD-PE plastic and closure LD-PE plastic)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Alturix Limited
287 Upper Fourth Street
Milton Keynes
MK9 1EH

8 MARKETING AUTHORISATION NUMBER(S)

PL 44490/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/04/2025

10 DATE OF REVISION OF THE TEXT

29/04/2025