SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Melatonin Consilient Health 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 mg of methyl parahydroxybenzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.
Clear colorless to yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melatonin is indicated for:

- Short-term treatment of jet lag in adults.
  The medicinal product is recommended to adult travellers flying across ≥5 time zones, particularly in an easterly direction, and especially if they have experienced jet lag symptoms on previous journeys. Travellers crossing 2-4 time zones can also use it if need be.
- 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

Adults with jet lag
The recommended dose is 1-5 mg one hour before bedtime at destination.
Recommended starting dose:
2 ml (equivalent to 2 mg)

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 Consilient health oral solution should not be taken before 20:00 hr or after 04:00 hr at destination.

Maximal recommended daily dose:
5 ml (equivalent to 5 mg) for a maximum of 5 days.

A maximum of 16 treatment cycles may occur per year.

Paediatric population with ADHD

Recommended starting dose:
1-2 ml (equivalent to 1-2 mg) 30 to 60 minutes before bedtime.

The dose should be adjusted individually to a maximum of 5 ml (equivalent to 5 mg) daily regardless of age. The lowest effective dose should be sought.

Maximal recommended daily dose:
5 ml (equivalent to 5 mg)

Limited data are available for up to 3 years of treatment. 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, especially if the treatment effect is uncertain, discontinuation attempts should be done regularly, e.g. once per year.

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

Special 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).

Renal impairment
The effect of any degree of renal impairment on the pharmacokinetics of melatonin has not been studied. Published data show elevated endogenous melatonin levels in patients with chronic renal failure. Caution should therefore be exercised when administering melatonin to patients with renal impairment (see section 5.2).

Hepatic impairment
There are no known studies on the use of melatonin in patients with hepatic impairment. Published data show markedly elevated endogenous melatonin levels in patients with hepatic impairment. Therefore, Melatonin Consilient Health is not recommended for patients with hepatic impairment (see section 5.2).

Children below 6 years of age
Melatonin Consilient Health is not recommended for children below 6 years with ADHD.

Method of administration
Oral use.
A measuring device, an oral syringe is packed together with the oral liquid dosage form. The capacity of the syringe is 5 ml with scale graduation of 0.2 ml.

Instruction for use
1. Remove the bottle cap.
2. Insert the syringe into the hole of the integrated adapter in the bottle opening and turn the bottle upside down. Measure the dose by slowly pulling out the plunger to the correct volume. Read the dose on the top of the piston. Turn the bottle right and remove the syringe.
3. The child should sit upright. Aim the tip of the syringe at the inside of the cheek. Slowly push in the plunger and allow the child to swallow naturally. Too fast administration of the medicine into the throat can cause discomfort.
4. Clean the inside of the syringe after each use.

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

Possible long-term effects of melatonin have been inadequately studied. 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.

Elderly
Exposure levels to melatonin after oral administration in young and moderately older adults are comparable. It is unclear if 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.

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

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

Drowsiness
Melatonin can cause drowsiness. Therefore, the drug should be used with caution if it is likely that the drowsiness may be associated with a safety risk.

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.

This medicine contains methyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

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. 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.

<u>Pharmacokinetic interactions</u>

<u>Agents that can increase plasma concentrations of melatonin</u>

CYP 1A inhibitors
Co-administration of melatonin with CYP1A2 inhibitors, such as fluvoxamine, quinolones, cimetidine, and 5- and 8-methoxypsoralen (5- and 8-MOP), may lead to increased melatonin exposure through inhibition of melatonin metabolism.

Fluvoxamine

Fluvoxamine is a potent inhibitor of CYP1A2 and to a lesser extent CYP2C. Fluvoxamine has been shown to increase serum concentrations of orally administered melatonin (17-fold higher AUC and 12-fold higher C_{max}). The combination should be avoided.

Cimetidine
Cimetidine is a weak inhibitor of CYP1A2. Cimetidine has been reported to increase plasma concentrations of melatonin. Caution should be exercised in patients treated with cimetidine.

Estrogens
Estrogens have been shown to increase melatonin concentrations by inhibiting CYP1A1 and CYP1A2 (4-5 fold increase in melatonin concentrations when used in combination with combined hormonal contraceptives). Caution must be exercised in patients treated with estrogens (e.g. hormonal contraceptives or hormonal substitution therapy).

Caffeine
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}).

Agents that can decrease plasma concentrations of melatonin

CYP1A inducers
Co-administration of melatonin with CYP1A2 inducers, such as carbamazepine, rifampicin and phenytoin, may result in reduced melatonin exposure through an increase in melatonin metabolism. Dose adjustment may be needed.

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

Pharmacodynamic interactions
Adrenergic agonists / antagonists, opiate agonists / antagonists, antidepressants, prostaglandin inhibitors, tryptophan and alcohol affect the endogenous secretion of melatonin in the epiphysis. Whether these interactions are of clinical significance is unknown.

Alcohol
Alcohol should not be taken with melatonin as it may reduce the effect of melatonin on sleep.

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

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
Case reports have reported that patients treated with melatonin and warfarin received concurrent changes in INR and prothrombin time. The combination of warfarin or other vitamin K antagonists with melatonin may require dose adjustment of the anticoagulant drugs and should be avoided.

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 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. 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. Animal studies are insufficient with respect to effects on fertility.

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; 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

Melatonin causes few and no serious adverse reactions in the short term, up to three months. There is limited documentation of long-term treatment with melatonin. Reported adverse reactions are mainly fatigue, dizziness and headache. However, these side effects are also common for placebo-treated patients.

Tabulated risks of adverse reactions

In the table below all adverse reactions are listed according to organ class and frequency: Very common (≥1/10), Common (≥100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥1/10 000, <1/1000), Very rare (<1/10 000), Not known (cannot be estimated from the available data).

Adverse reactions are presented within each frequency in order of decreasing seriousness.

Table 1

System organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Rare	Herpes Zoster
Blood and lymphatic system disorders	Rare	Leukopenia, thrombocytopenia
Immune system disorders	Not known	Hypersensitivity reaction
Metabolism and nutrition disorders	Rare	Hypertriglyceridaemia, hypocalcaemia, hyponatraemia
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, memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, paraesthesia
Eyes	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 flush
Gastrointestinal disorders	Uncommon	Abdominal pain, abdominal pain upper, dyspepsia, mouth ulceration, dry mouth, nausea
	Rare	Gastro-esophageal 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	Asthenia, 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 pediatric population a low frequency of generally mild adverse reactions has been reported. The adverse events have not been significantly different in children who has received placebo compared to

children who received melatonin. The most common adverse effects were headache, hyperactivity, vertigo and abdominal pain. No serious adverse 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

Administration of repeated daily doses of up to 300 mg melatonin without any clinically significant side effects has been reported in the literature.

Drowsiness can be expected in case of overdose. Due to the short half-life of melatonin, complete elimination of melatonin from the body is expected within 12 hours of ingestion. Physicians should assess whether common overdose measures should be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoeleptics, melatonin receptor agonists, ATC code: N05CH01.

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone produced by the epiphysis and structurally related to serotonin. Melatonin is involved in controlling the circadian rhythm and adaptation to the light-dark cycle. It is also associated with a sedative effect and an increased propensity for sleep.

Serum concentrations of endogenous melatonin vary over the day. Melatonin levels increase during the dark hours of the day with maximum serum concentrations between 02 and 04 in the morning (Srinivasan 2009; Tordjman 2017). Thereafter, serum levels of melatonin gradually decrease. Only a small amount of melatonin is excreted during the light hours of the day.

Mechanism of action
The activity of melatonin on MT1, MT2 and MT3 receptors is thought to contribute to its sleep-promoting properties since these receptors (especially MT1 and MT2) are involved in the regulation of diurnal rhythm and sleep regulation.
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 de-synchronisation.

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. Eight of ten 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. 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 re-synchronisation of circadian rhythmicity/jet lag, melatonin should not be taken before 20:00 hr or after 04:00 hr at destination.

Adverse reactions reported in jet lag studies involving melatonin doses of 0.5 to 8 mg were typically mild, and often difficult to distinguish from symptoms of jet lag. Transient drowsiness/sedation, headache 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.

Paediatric population
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

The pharmacokinetic parameters below are based on adult documentation.

Absorption
The absorption of oral melatonin is almost complete in adults. The bioavailability is 10–35% due to extensive first-pass metabolism of melatonin. Maximum concentration of orally administered melatonin occurs after 15–90 minutes (median T_{max} = 52 min). Based on limited data with high inter-subject variability, food intake may increase exposure and maximum plasma concentration of melatonin, likely not to a clinically relevant extent.

Distribution
Plasma protein binding of melatonin in vitro is approximately 60%. The mean volume of distribution is 1.2 and 1.8 L/kg (84 and 126 L for a 70 kg subject) for subjects receiving 10 mg and 0.5 µg/kg intravenous doses of melatonin respectively.

Biotransformation
Melatonin is mainly eliminated by hydroxylation to 6-hydroxymelatonin in the liver, primarily mediated by CYP1A2 (to a lesser extent by CYP1A1). Quantitatively less important is O-demethylation to N-acetyl-5-hydroxytryptamine mediated by CYP2C19. Melatonin metabolites are mainly eliminated by the urine, ~ 90% as sulphate and glucuronide conjugates of 6-hydroxymelatonin. Less than 1% of the melatonin dose is excreted unchanged in the urine.

Elimination
Melatonin has a short half-life (t½) of between 30 and 60 minutes. The half-life, on average, is comparable or slightly shorter in children compared to adults.

Gender
Higher exposure and maximum plasma concentrations have been reported in women compared to men who have received melatonin orally, however a large variability in the pharmacokinetics is observed. Plasma melatonin half-life does not appear to be significantly different in men and women. Dose adjustment for women are not necessary.

Linearity
Maximum concentration and exposure of melatonin after oral dosing increases proportionally to the dose from 0.25 up to 10 mg.

Special patient groups

Renal impairment
The effect of renal impairment on the pharmacokinetics of melatonin administered has not been studied. However, published data show elevated endogenous melatonin levels in patients with chronic renal failure (see section 4.2).

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

Elderly
In a comparative study of the levels of serum melatonin with and without administration of exogenous melatonin, lower concentrations were found in moderately older adults without treatment, while a trend toward higher concentrations was observed compared to healthy younger adults after treatment. The observed difference between the age groups was not statistically significant. The same dose of melatonin can be recommended to older adults and younger adults.

5.3 Preclinical safety data

Current studies on safety pharmacology, general toxicity, genotoxicity and carcinogenicity, did not show any particular risks to humans.

In toxicological studies, effects were seen only at high exposures / at exposures significantly higher than clinical exposures. These effects are therefore considered to have no clinical relevance.

In the reproductive toxicology studies, oral administration of melatonin to pregnant female rats did not lead to any effects on the offspring, with regard to fetal survival, skeletal and visceral anomalies or birth weight. Administration of melatonin to mice early in their pregnancy did not generate any apparent reproductive toxicities.
There are no safety studies in juvenile animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol (E422)
Sorbic acid
Methyl parahydroxibenzoate (E218)
Sodium hydroxide (for pH adjustment)

Water, purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months. Shelf life after first opening: 6 months.

6.4 Special precautions for storage

Do not store above 30°C. Store in original bottle in order to protect from light.

6.5 Nature and contents of container

Amber glass bottle 30 ml, 100 ml,150 ml or 200 ml. The 30 ml, 100 ml, 150 ml & 200 ml bottles with a child-resistant white polypropylene and HDPE/LDPE cap with an intergrated syringe adapter. An oral syringe is packed together with the bottle. The capacity of the syringe is 5 ml with scale graduation of 0.2 ml.

6.6 Special precautions for disposal and other handling

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

Consilient Health Ltd.,
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8. MARKETING AUTHORISATION NUMBER(S)

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