Reference
1. Melatonin Consilient Health Summary of Product Characteristics

Abbreviated Prescribing Information – for full prescribing information, including side effects, precautions and contra-indications, see Summary of Product Characteristics (SmPC).

Product name: Melatonin Consilient Health 1 mg/ml oral solution. **Composition:** 1ml oral solution contains 1mg melatonin. **Indications:** (1) 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. (2) Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient. **Dosage and administration:** *Adults with jet lag:* Recommended dose is 1-5 mg one hour before bedtime at destination. Recommended starting dose is 2ml (equivalent to 2mg). 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 is 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 is 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 is 5 ml (equivalent to 5 mg). Limited data are available for up to 3 years of treatment. After at least 3 months of treatment, evaluate treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. Monitor 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, attempt discontinuation regularly, e.g. once per year. If the sleep disorder has started during treatment with medicinal products for ADHD, consider dose adjustment or switching to another product. 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. 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. Exercise caution when administering melatonin to patients with renal impairment. 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. Children below 6 years of age: Melatonin Consilient Health is not recommended for children below 6 years with ADHD. Oral use; see Summary of Product Characteristics for full administration details. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Warnings and Precautions:** 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. Drowsiness: Melatonin can cause drowsiness. Use 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'. **Interaction with other medicinal products:** Agents that can increase plasma concentrations of melatonin: 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 is a potent inhibitor of CYP1A2 and to a lesser extent CYP2C, and has been shown to increase serum concentrations of orally administered melatonin (17-fold higher AUC and 12-fold higher C_{max}). Avoid this combination. Cimetidine is a weak inhibitor of CYP1A2 and has been reported to increase plasma concentrations of melatonin. Exercise caution in patients treated with cimetidine. 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). Exercise caution in patients treated with estrogens. Caffeine is a substrate for CYP1A2 and 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: 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. 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). Alcohol should not be taken with melatonin as it may reduce the effect of melatonin on sleep. Melatonin may enhance the sedative properties of benzodiazepine and nonbenzodiazepine hypnotics such as zaleplon, zolpidem and zopiclone. Melatonin may reduce the hypotensive effect of nifedipine, so caution should be exercised in this combination and dose adjustment of nifedipine may be needed. Case reports of patients treated with melatonin and warfarin have reported 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. **Fertility, pregnancy and lactation:** There are no or limited amount of data for the use of melatonin in pregnant women; Melatonin is not recommended during pregnancy or in women and adolescents of childbearing potential not using contraception. There is insufficient data on the excretion of melatonin/metabolites in human milk; a risk for the breastfed child cannot be excluded. Melatonin should not be used during breast-feeding. **Effects on ability to drive and use machines:** Melatonin has moderate effect on the ability to drive and use machines and 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. **Undesirable effects:** Common (≥100, <1/10): Headache; somnolence. Uncommon (≥ 1/1,000 to < 1/100: Irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety, migraine, lethargy, psychomotor hyperactivity, dizziness, hypertension, abdominal pain, abdominal pain upper, dyspepsia, mouth ulceration, dry mouth, nausea, hyperbilirubinaemia, Dermatitis, night sweats, pruritus, rash, pruritus generalised, dry skin, pain in extremity, glycosuria, proteinuria, menopausal symptoms, asthenia, chest pain, liver function test abnormal, weight increased. Rare (≥ 1/10,000 to < 1/1,000): Herpes zoster, leukopenia, thrombocytopenia, hypertriglyceridaemia, hypocalcaemia, hyponatraemia, mood altered, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, libido increased, depressed mood, depression, syncope, memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, paraesthesia, visual acuity reduced, vision blurred, lacrimation increased, vertigo positional, vertigo, angina pectoris, palpitations, hot flush, 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, eczema, erythema, hand dermatitis, psoriasis, rash generalised, rash pruritic, nail disorder, arthritis, muscle spasms, neck pain, night cramps, polyuria, haematuria, nocturia, priapism, prostatitis, fatigue, pain, thirst, hepatic enzyme increased, blood electrolytes abnormal, laboratory test abnormal. Not known (cannot be estimated from the available data): Hypersensitivity reaction, angioedema, oedema of mouth, tongue oedema, galactorrhea. **NHS price:** £ 86.67 / 100ml pack. **Legal classification:** POM. **MA number:** PL 24837/0133. **Marketing Authorisation Holder:** Consilient Health Limited, 5th Floor, Beaux Lane House, Mercer Street Lower, Dublin 2, Ireland. **Further information is available on request from:** Consilient Health (UK) Ltd, No.1 Church Road, Richmond upon Thames, Surrey, TW9 2QE or drugsafety@consilienthealth.com **Date of preparation of PI: January 2022 Job bag number: CORP-CH-752**

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Consilient Health (UK) Ltd, No. 1 Church Road, Richmond upon Thames, Surrey TW9 2QE UK or drugsafety@consilienthealth.com

Melatonin
Consilient Health
1mg/1ml oral solution