Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Voquily 1 mg/ml oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 1 mg of melatonin.

Excipients with known effect:
Sorbitol: 140 mg per 1 ml dose.
Propylene glycol: 150 mg per 1 ml dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution.
Clear, colourless to yellowish solution with characteristic strawberry odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Voquily is indicated for:

- Short-term treatment of jet lag in adults.
- Sleep onset insomnia in children and adolescents aged 6-17 years with attention-deficit hyperactivity disorder (ADHD) where sleep hygiene measures have been inadequate.

4.2 Posology and method of administration

Posology

Adults
For the short-term treatment of jet lag in adults:

The standard dose is 3 mg (3 ml) daily for a maximum of 5 days. The dose may be increased to 5 mg (5 ml) for a maximum of 5 days, if the standard dose does not adequately alleviate symptoms.
The dose that adequately alleviates symptoms should be taken for the shortest period.

The first dose should be taken on arrival at destination at the habitual bed-time (at local time).

Due to the potential for incorrectly timed intake of melatonin to have no effect, or an adverse effect, on re-synchronisation following jet lag, Voquily should not be taken before 20:00 hr or after 04:00 hr at destination.

Voquily may be taken for a maximum of 16 treatment periods per year.

As alcohol can impair sleep and potentially worsen certain symptoms of jet lag (e.g. headache, morning fatigue, concentration) it is recommended that alcohol is not consumed when taking Voquily (see section 4.5).

Paediatric population
The efficacy and safety of melatonin for use in jet-lag has not been established in children under 18 years.

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

The recommended starting dose is 1-2 mg (1-2 ml), 30-60 minutes before bedtime. The dose may be adjusted on an individual basis to a maximum of 5 mg per day regardless of age of the child. The lowest effective dose should be taken for the shortest period.

Limited data is available for up to 3 years of treatment. After at least 3 months of treatment, the doctor should evaluate the treatment effect and consider discontinuing the treatment if no clinically relevant treatment effect is seen. The patient should be monitored regularly (at least every 6 months) to check that Voquily is still the most appropriate treatment. During ongoing treatment, especially if the treatment effect is uncertain, discontinuation attempts should be done regularly, at least once a year.

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

Children under 6 years of age with ADHD
The safety and efficacy of Voquily in children aged 0 – 6 years have not been established.

Other population

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 (see Section 5.2).

Renal impairment
There is only limited experience regarding the use of Voquily in patients with renal impairment. Caution should be exercised if melatonin is used by patients with renal impairment. Voquily is not recommended for patients with severe renal impairment (see Section 5.2).

Hepatic impairment
There is no experience regarding the use of Voquily in patients with hepatic impairment. Limited data indicate that plasma clearance of melatonin is significantly reduced in patients with liver cirrhosis. Voquily is not recommended in patients with hepatic impairment (see Section 5.2).

Impaired glucose tolerance
Intake of melatonin with carbohydrate-rich meals may impair blood glucose control for several hours (see Section 4.4).

Method of administration

Voquily is for oral use only.

Voquily should be taken with a glass of water.

Food can enhance the increase in plasma melatonin concentration. It is recommended that Voquily is administered on an empty stomach and food is not consumed 1 h before and 1 h after intake of Voquily (see Section 5.2).

A 10 ml graduated oral syringe with intermediate graduations of 0.5 ml and a "Press- In" Bottle Adapter (PIBA) are provided with the product.

1. Open the bottle and at first use insert the PIBA.
2. Insert the syringe into the PIBA and draw out the required volume from the inverted bottle.
3. Remove the filled syringe from the bottle in the upright position
4. Discharge the syringe contents into the mouth.
5. Rinse the syringe and replace the cap on the bottle (PIBA remains in place).

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

When treating insomnia in children and adolescents, melatonin should only be administered after other treatable causes of insomnia have been ruled out by appropriate specialist investigation and non-pharmacological measures have been inadequate.

Melatonin may cause drowsiness. Voquily 1mg/ml oral solution should be used with caution if the effects of drowsiness are likely to be associated with a risk to patient safety (see section 4.7).

Epilepsy
Melatonin has been reported to both increase and decrease seizure frequency in patients experiencing seizures (e.g. epileptic patients). Caution should be exercised when prescribing to patients with epilepsy and/or with multiple neurological defects and/or with concomitant medications that could increase seizure frequency.

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

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

Renal/Hepatic impairment
Only limited data are available on the safety and efficiency of melatonin in patients with renal impairment or hepatic impairment. Voquily is not recommended for use in patients suffering from severe renal impairment or hepatic impairment.

Voquily contains sorbitol and propylene glycol:
This medicine contains 140 mg sorbitol in each ml. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

This medicine contains 150 mg propylene glycol in each ml.

4.5 Interaction with other medicinal products and other forms of interaction

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.
CYP1A2 inhibitors

- 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 indicated 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.
- Caffeine, like melatonin, is metabolised by CYP1A2. Caffeine has been shown to increase serum concentrations of orally administered melatonin.

CYP1A2 inducers

- 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

Benzodiazepine-like hypnotics
Melatonin may enhance the sedative effect of benzodiazepines (e.g. midazolam, temazepam) and non-benzodiazepine hypnotics (e.g. zaleplon, zolpidem, zopiclone). In a study of jet lag therapy the combination of melatonin and zolpidem resulted in a higher incidence of morning sleepiness, nausea, and confusion, increased impairment of attention, memory and coordination as well as reduced activity during the first hour after getting up, compared to zolpidem alone. The use of melatonin in combination with these drugs is not recommended.

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
Melatonin may increase the anticoagulation activity of warfarin. The combination of warfarin or other vitamin K antagonists with melatonin may require dose adjustment of the anticoagulant drugs and should be avoided.

Thioridazine/Imipramine
Melatonin may enhance the feelings of drowsiness and inability to perform tasks when administered with thioridazine or imipramine.

Alcohol
Alcohol is a sedative with the ability to alter physical and mental functions. There is a potential for patients to have enhanced drowsiness when alcohol is co-administered with melatonin (see section 4.2).

Beta-blockers
Beta-blockers may suppress the endogenous melatonin but the clinical relevance of this is unknown when administering exogenous melatonin.

NSAIDs
Some NSAIDs, e.g. aspirin, ibuprofen, may reduce the endogenous secretion of melatonin, but the clinical relevance of this is unknown when administering exogenous melatonin.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data for the use of melatonin in pregnant women. Exogenous melatonin readily crosses the human placenta.

Animal studies are insufficient with respect to reproductive toxicity (see Section 5.3).

Voquily is not recommended during pregnancy or in women of childbearing potential not using contraception.

Breast-feeding
Endogenous melatonin is secreted in human milk.

Available pharmacodynamic / toxicological data in animals have shown excretion of exogenous melatonin / metabolites in milk (see Section 5.3).

A risk to the suckling child cannot be excluded.

Voquily should not be used during breast-feeding.

Fertility
High doses of melatonin impaired male and female fertility in animals. The relevance of these data for human fertility is unknown.

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 Voquily is not recommended prior to driving and using machines.

4.8 Undesirable effects

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

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					hyper-sensitivity reaction
Metabolism and nutrition disorders				hypertriglyceridaemia, hypocalcaemia, hyponatraemia	
Psychiatric disorders			irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety	mood altered, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, libido increased, depressed mood, depression	
Nervous system disorders		headache, somnolence	migraine, lethargy, psychomotor hyperactivity, dizziness	syncope (fainting), memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, paraesthesia	drowsiness sedation
Eye disorders				visual acuity reduced, vision blurred, lacrimation increased	
Ear and labyrinth disorders				vertigo positional, vertigo	
Cardiac disorders				angina pectoris, palpitations	
Vascular disorders			hypertension	hot flushes	

Gastrointestinal disorders			abdominal pain, upper abdominal pain, dyspepsia, mouth ulceration, dry mouth, nausea	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			Hyperbilirubinaemia		
Skin and subcutaneous tissue disorders			dermatitis, night sweats, pruritus, rash, pruritus generalised, dry skin	eczema, erythema, hand dermatitis, psoriasis, rash generalised, rash pruritic, nail disorder	angioedema, tongue oedema, oedema of the mouth
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	
Laboratory and other examinations			liver function test abnormal, weight increased	hepatic enzyme increased, blood electrolytes abnormal, laboratory test abnormal	

Paediatric population
In the paediatric population, a low frequency of generally mild side effects have been reported. The number of side effects did not differ significantly between children who received placebo and children who received melatonin. The most common side effects were headache, hyperactivity, dizziness and abdominal pain. No serious side effects have been observed.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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.

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 and circadian rhythms in general.

Pharmacodynamic effects
Melatonin has a hypnotic / sedative effect and increases propensity for sleep. Melatonin administered earlier or later than the nocturnal peak in melatonin secretion can, respectively, advance or delay the circadian rhythmicity of melatonin secretion. Administration of melatonin at bedtime (between 22:00 and 24:00 hr) at destination following rapid transmeridian travel (aircraft flight) hastens resynchronisation of circadian rhythmicity from 'departure time' to 'destination time', and ameliorates the collection of symptoms known as jet lag that are a consequence of such de- synchronisation.

Clinical efficacy and safety
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 (body clock) than to delay it, as required following westward travel. Clinical trials have found melatonin to reduce patient-assessed overall symptoms of jet lag by ~ 44%, and to shorten the duration of jet lag. In 2 studies of flights over 12 time zones melatonin effectively reduce the duration of jet lag by ~ 33% (Petrie 1989 et al, Cardinali et al 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.

Adverse effects 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 with ADHD and sleep disorders
Melatonin treatment has been studied in a 4-week randomised, double-blind, placebo- controlled study conducted in 105 stimulant-free children 6 to 12 years, 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.

5.2 Pharmacokinetic properties

Melatonin is a small, amphiphilic molecule (molecular weight 232 g/mol) active in its parent form. Melatonin is synthesised in the human body from tryptophan via serotonin. Small quantities are obtained via diet. Data summarised below are from studies that generally involved healthy men and women, primarily young and middle- aged adults.

Absorption

Orally administered melatonin is almost completely absorbed. Oral bioavailability is 10-35%, owing to first-pass metabolism of melatonin. Plasma T_{max} is ~ 20 minutes. A 3 mg dose of immediate- release melatonin raises plasma melatonin C_{max} to ~ 8700 pg/mL, which is ~60-times the nocturnal (endogenous) plasma melatonin C_{max} in young adults and ~170 times in older subjects, although both endogenous- and exogenous C_{max} show considerable inter-individual variation.

Data on the effect of intake of food at or around the time of intake of melatonin on its pharmacokinetics are limited, though suggest that concomitant food intake may increase bioavailability almost 2-fold. Food appears to have a limited effect on T_{max} for immediate-release melatonin. This is not expected to affect the efficacy or safety of melatonin, however, it is recommended that food is not consumed approximately 1 h before and 1 h after intake of melatonin.

Distribution

The protein binding of melatonin is approximately 50 – 60%. Melatonin primarily binds to albumin, though also binds alpha1-acid glycoprotein; binding to other plasma proteins is limited. Melatonin rapidly distributes from the plasma into and out of most tissues and organ, and readily crosses the brain-blood barrier. Melatonin readily crosses the placenta. The level in umbilical blood of full-term babies closely correlates with that of their mother following ingestion of a 3 mg dose.

Biotransformation

Melatonin is mainly metabolised by the liver. Experimental data suggest that the cytochrome P450 enzymes CYP1A1 and CYP1A2 are primarily responsible for melatonin metabolism, with CYP2C19 of minor importance. Melatonin is primarily metabolised to 6-hydroxymelatonin (constituting ~ 80 – 90% of melatonin metabolites recovered in the urine). N-acetylserotonin appears to be the primary minor metabolite (constituting ~ 10% of melatonin metabolites recovered in the urine). Melatonin metabolism is very rapid, with plasma 6-hydroxymelatonin level rising within minutes of exogenous melatonin entering the systemic circulation. 6- hydroxymelatonin undergoes sulphate conjugation (~ 70%) and glucuronide conjugation (~ 30%) prior to excretion.

Elimination

Plasma elimination half-life (T½) is ~ 45 minutes (normal range ~ 30 – 60 minutes) in healthy adults. The half-life, on average, is comparable or slightly shorter in children compared to adults. Melatonin metabolites are mainly eliminated by the urine, ~ 90% as sulphate and glucuronide conjugates of 6-hydroxymelatonin. Less than ~ 1% of a melatonin dose is excreted unchanged in urine.

Linearity

Plasma melatonin C_{max} and AUC increase in a directly proportional, linear manner for oral doses of immediate-release melatonin in the range 1 – 10 mg, whereas Tmax and plasma T½ remain constant.

Gender

Limited data suggest there is a potential of an increase in C_{max} for older women compared to men. A wide variability in C_{max} between different members of the same sex has also been observed. However, no pharmacodynamic differences between males and females were found despite differences in blood levels. Dose adjustment for women is not necessary.

Special populations

Older people

Night-time endogenous melatonin plasma concentration is lower in the elderly compared to young adults. Limited data for plasma- 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 tend to be greater in the elderly.

Hepatic impairment

Limited data indicate that daytime endogenous blood melatonin concentration is markedly elevated in patients with liver cirrhosis, probably due to reduced clearance (metabolism) of melatonin. Serum T½ for exogenous melatonin in cirrhosis patients was double that of controls in a small study. As the liver is the primary site of melatonin metabolism, hepatic impairment can be expected to result in increased exposure to exogenous melatonin.

Renal impairment

As melatonin is primarily excreted as metabolites in the urine, plasma levels of melatonin metabolites can be expected increase in patients with more advanced renal impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of single and repeated dose toxicity, genotoxicity, and carcinogenic potential.

The data regarding reproductive toxicology is limited.

Embryo-foetal development studies in rats and rabbits did not show direct or indirect harmful effects with respect to pregnancy, foetal survival, foetal body weight, or incidences of foetal malformations/variations.

Results from studies of prenatal and postnatal development in rats indicate that melatonin administration affects the hormonal level and sexual maturation in the offspring.

Data from animal studies indicate that melatonin is transmitted to the foetus via the placenta.

There are no safety studies on juvenile animals

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol (E1520)
Sorbitol liquid (non crystallising) (E420)
Sucralose (E955)
Strawberry flavour (including propylene glycol (E1520))
Hydrochloric acid (for pH adjustment) (E507)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
After first opening: use within 6 months.

6.4 Special precautions for storage

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

This medicinal product does not require any special temperature storage conditions

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber glass bottles containing 60 ml or 150 ml oral solution, closed with an HDPE child-resistant, tamper-evident screw cap with an LDPE liner. An LDPE, 10 ml graduated oral syringe with intermediate graduations of 0.5 ml and an LDPE, "press-in" syringe/bottle adaptor are provided.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Clinigen Healthcare B.V.
Schiphol Boulevard 359
WTC Schiphol Airport
D Tower 11th floor
1118BJ Schiphol
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA22701/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th August 2022

10 DATE OF REVISION OF THE TEXT