SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Neomel 1mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 1 mg of melatonin.

Excipients with known effect:

Sorbitol: 300 mg

Propylene glycol: 150 mg

Methyl parahydroxybenzoate: 1.75 mg

Propyl parahydroxybenzoate: 0.25 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

A clear, colourless, slightly viscous liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Neomel is indicated for short-term treatment of jet-lag in adults only.

4.2 Posology and method of administration

Posology

The standard dose is 3 mg daily for a maximum of 5 days. The dose may be increased to 6 mg 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.

Due to the potential for incorrectly timed intake of melatonin to have no effect, or an adverse effect, on re-synchronisation following jet-lag, Neomel should not be taken before 20:00 hr or after 04:00 hr at destination.
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 h before and 2 h after intake of Neomel.
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 Neomel.
Neomel may be taken for a maximum of 16 treatment periods per year.

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

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

Hepatic impairment

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

Paediatric population

The safety and efficacy of Neomel in children and adolescents aged 0 – 18 years have not been established. Neomel should not be used in children and adolescents due to safety and efficacy concerns (see Sections 4.4 and 5.1).

Method of administration

Neomel is for oral use only.
A 5 ml graduated oral syringe with intermediate graduations of 0.5 ml and a “Press-In” Bottle Adapter (PIBA) is provided with the product.

1. Remove the child-resistant, tamper evident cap from the bottle by pushing it down and turning it anti-clockwise. **(Figure 1)**
2. Push the PIBA into the neck of the product bottle **(Figure 2)**

3. With the plunger of the syringe pressed completely down, insert the syringe into the PIBA **(Figure 3)** and draw out the required volume from the inverted bottle **(Figure 4)**
4. Remove the filled syringe from the bottle in the upright position **(Figure 5)**
5. Discharge the syringe contents into the mouth **(Figure 6)**
6. Wash the syringe inside and out by rinsing in water and replace the cap on the bottle **(Figure 7)**

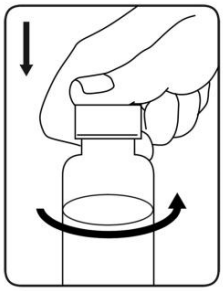


Figure 1

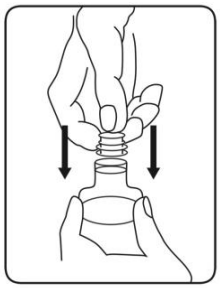
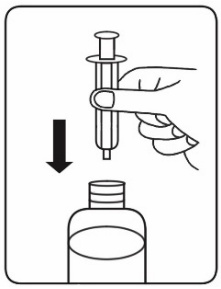


Figure 2



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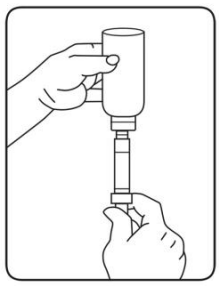

Figure 4

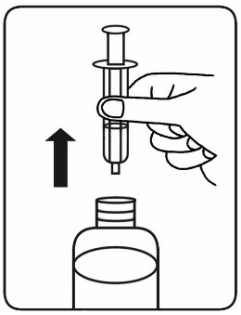

Figure 5

Figure 6

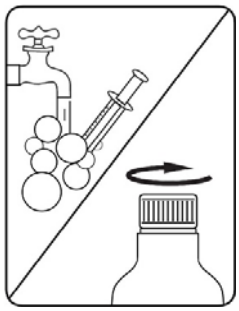

Figure 7

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. Neomel should be used with caution if the effects of drowsiness are likely to be associated with a risk of patient safety**.**

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

Occasional case reports have described exacerbation of an autoimmune disease in patients taking melatonin. There are no data regarding use of Neomel in patients with autoimmune diseases. Neomel 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. Neomel 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.

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

Dose equivalence and conversion for melatonin

Caution is advised when switching between immediate-release formulations as the peak plasma-melatonin concentration may be higher with the oral solution than with tablets.

Paediatric population

The safety and efficacy of Neomel in children and adolescents aged 0 – 18 years have not been established. Neomel should not be used in children and adolescents due to safety and efficacy concerns (see Section 5.1).

This medicine contains methyl parahydroxybenzoate and propyl 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’.

This medicine contains sorbitol and propylene glycol in each ml. This medicinal product contains sorbitol. 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.

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 Cmax) 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 CYP2D.
- Caution should be exercised in patients receiving oestrogen therapy (e.g. in the form of contraceptives or hormone replacement therapy), since oestrogens 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. 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, and reduced activity during the first hour after getting up, compared to zolpidem alone.
- Melatonin may affect the anticoagulation activity of warfarin.

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).

Neomel 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 milk (see Section 5.3).

A risk to the suckling child cannot be excluded.

Neomel 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).

Neomel 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 Neomel 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 reported 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

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).

System Organ class	**Frequency**	**Adverse reaction**
Infections and infestations	Rare	Herpes zpster
Blood and lymphatic systemdisorders	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 activity reduces, 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	Meopausal symptoms
	Rare	Priapism, prostatitis
	Not known	Galactorrhea
General disorders and administration site conditions	Uncommon	Astenia, chest pain
	Rare	Fatigue, pain, thirst
Investigations	Uncommon	Liver function test abnormal, weight increased
	Rare	Hepatic enzyme increased, blood electrolytes abnormal, laboratory test abnormal

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Melatonin

ATC code: N05CH01

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 00:00 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 jetlag 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 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%. 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. Transient drowsiness / sedation, headache, and dizziness / disorientation were reported; these same adverse effects, plus nausea, are those typically associated with short-term use of melatonin in reviews of the safety of melatonin in humans.

Paediatric population

The safety and efficacy of melatonin in children and adolescents aged 0 – 18 years have not been established. Neomel should not be used in children and adolescents aged 0 – 18 years due to safety concerns. Specifically, this is due to the fact that interference with the function of endogenous melatonin on the development of the hypothalamic-pituitary-gonadal axis cannot be excluded.

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 ~ 15%, owing to first-pass metabolism of ~ 85%. Plasma T_{max} is ~ 50 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} 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 Tmax for immediate-release melatonin. This is not expected to affect the efficacy or safety of Neomel; however, it is recommended that food is not consumed approximately 2 h before and 2 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, 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. 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. 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 3 – 6 mg whereas Tmax and plasma T½ remain constant.

Gender

Limited data suggest that C_{max} and AUC following ingestion of immediate release melatonin may be higher (potentially roughly double) in women compared to men, however a large variability in the pharmacokinetics is observed. Plasma melatonin half-life does not appear to be significantly different in men and women.

Special populations

Older people

Night-time endogenous melatonin plasma concentration is lower in the elderly compared to young adults. 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 (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

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.

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 postpartum. 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

purified water, sorbitol solution [Sorbitol (E420)], propylene glycol (E1520), tri-sodium citrate (E331), hydroxyethyl cellulose (E1525), methyl hydroxybenzoate [Methyl parabens (E218)], propyl hydroxybenzoate [Propyl parabens (E216)]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

Bottle once opened: up to 150 days

6.4 Special precautions for storage

Store below 30ºC

Do not store above 25ºC after first opening of the bottle

6.5 Nature and contents of container

Amber, PET plastic bottle of nominal 160 ml capacity, safely closed with a polypropylene child-resistant, tamper-evident screw cap. A polypropylene, CE marked 5 ml graduated syringe, with intermediate graduations of 0.5 ml and syringe/bottle LDPE adapter is also provided.

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

Neoceuticals Limited
Level 18,
40 Bank Street,
Canary Wharf,
London,
E14 5NR,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 36116/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/11/2024

10 DATE OF REVISION OF THE TEXT

17/04/2025