1. NAME OF THE MEDICINAL PRODUCT

Melatonine Orifarm 2 mg, filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film-coated tablet contains 2 mg melatonin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White/off-white to beige, biconvex, circular shaped film-coated tablet with a score line and “2” on one side. Diameter: 8 mm.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term treatment of jet-lag in adults (see section 5.1).

4.2 Posology and method of administration

Posology
The standard dose is 2 mg (1 tablet) daily for a maximum of 5 days. The dose may be increased to 4 mg (2 tablets taken together) or up to 6 mg (3 tablets taken together) 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 the destination at the habitual bed-time.

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, Melatonine Orifarm should not be taken before 20:00 hr or after 04:00 hr at destination.

Melatonine Orifarm 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 melatonin in patients with renal impairment. Caution should be exercised if melatonin is used by patients with renal impairment. Melatonine Orifarm is not recommended for patients with severe renal impairment (see section 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 liver cirrhosis. Melatonine Orifarm is not recommended in patients with moderate or severe hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of Melatonine Orifarm in children and adolescents aged 0 to 18 years have not been established. Melatonine Orifarm should not be used in children and adolescents because of safety and efficacy concerns (see section 5.1).

Method of administration
Oral use.

Food can enhance the increase in plasma melatonin concentration (see section 5.2). Intake of melatonin with carbohydrate-rich meals may impair the 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 Melatonine Orifarm.
Alcohol should not be consumed when taking Melatonine Orifarm (see section 4.5).

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

Melatonin may increase the seizure frequency in patients experiencing seizures (e.g. epileptic patients). Patients suffering from seizures must be informed about this possibility before using Melatonine Orifarm. 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 melatonin in patients with autoimmune diseases. Melatonine Orifarm 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 the blood glucose control for several hours. Melatonine Orifarm should be taken at least 2 hours before and at least 2 hours after a meal; ideally at least 3 hours after a 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. Melatonine Orifarm is not recommended for use in patients suffering from severe renal impairment or moderate or severe hepatic impairment.

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.

- Caution should be exercised 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 should be exercised in patients taking 5 or 8-methoxypsoralen (5 or 8-MOP), as this agent increases melatonin levels by inhibiting its metabolism.
- Caution should be exercised in patients taking cimetidine, since this agent increases plasma melatonin levels by inhibiting its metabolism by CYP2D.
- 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.
- 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.
- 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 Melatonine Orifarm.
- Melatonin may affect the anticoagulation activity of warfarin.

Paediatric population
Interaction studies have only been performed in adults.

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).
Melatonine Orifarm is 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 in milk (for details see section 5.3).

A risk to the breast-fed newborn, infant and child cannot be excluded. Melatonine Orifarm 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). Melatonine Orifarm is not recommended in women and men planning pregnancy.

4.7 Effects on ability to drive and use machines

Melatonine Orifarm has moderate influence on the ability to drive and use machines. Melatonin may cause drowsiness and may decrease alertness for several hours, therefore use of Melatonine Orifarm is not recommended prior to driving or using machines.

4.8 Undesirable effects

Summary of the safety profile
Drowsiness/sleepiness, headache and dizziness/disorientation are the most frequently reported adverse reactions when melatonin is taken on a short-term basis to treat jet-lag. Drowsiness, headache, dizziness, and nausea are also the adverse reactions 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, the undesirable effects are presented in order of decreasing seriousness.

Blood and lymphatic system disorders Rare (≥1/10,000 to <1/1,000)	Leukopenia, thrombocytopenia
Immune system disorders Not known (cannot be estimated from the available data)	Hypersensitivity reaction
Metabolism and nutrition disorders Rare (≥1/10,000 to <1/1,000) Not known (cannot be estimated from the available data)	Hypertriglyceridemia Hyperglycaemia
Psychiatric disorders Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	Irritability, nervousness, restlessness, abnormal dreams, anxiety Mood altered, aggressive behaviour, disorientation, libido increased
Nervous system disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	Headache, somnolence Dizziness Syncope, memory impairment, restless legs syndrome, paraesthesia
Eye disorders Rare (≥1/10,000 to <1/1,000)	Visual acuity reduced, vision blurred, lacrimation increased
Cardiac disorders Rare (≥1/10,000 to <1/1,000)	Palpitations

Vascular disorders Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	 Hypertension Hot flushes
Gastrointestinal disorders Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	 Abdominal pain, upper abdominal pain, dyspepsia, oral ulcers, dry mouth, nausea Vomiting, flatulence, salivary hypersecretion, halitosis, gastritis
Skin and subcutaneous tissue disorders Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000) Not known (cannot be estimated from the available data)	 Pruritus, rash, dry skin Nail disorder Tongue oedema, oral mucosa swollen
Musculoskeletal and connective tissue disorders Rare (≥1/10,000 to <1/1,000)	 Arthritis, muscle spasms
Renal and urinary disorders Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	 Glycosuria, proteinuria Polyuria, haematuria
Reproductive system and breast disorders Rare (≥1/10,000 to <1/1,000) Not known (cannot be estimated from the available data)	 Priapism, prostatitis Galactorrhoea
General disorders and administration site conditions Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	 Chest pain, malaise Thirst
Investigations Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	 Weight increased Blood electrolytes 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 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 (3,000 – 6,600 mg) for several weeks.
General supportive measures should be employed. Gastric lavage and administration of activated charcoal can be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: melatonin receptor agonists, 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 of 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
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. Clinical trials in subjects flying across more than 5 time zones have found melatonin to reduce patient-assessed overall symptoms of jet-lag by ~ 44 %, and to shorten the duration of jet-lag. The effect is more pronounced after eastward travel than westward travel. 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

The safety and efficacy of melatonin in children and adolescents aged 0 – 18 years have not been established. Melatonine Orifarm 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 the diet. The 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 approximately 15 %, owing to a first-pass metabolism of approximately 85 %. Plasma t_{max} is apporximately 50 minutes. A 3 mg dose of immediate-release melatonin raises plasma melatonin C_{max} to approximately 3,400 pg/mL, which is around 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 the absorption 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 Melatonine Orifarm, 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 organs, and readily crosses the blood-brain barrier. Melatonin readily crosses the placenta. The level in umbilical blood of full-term babies closely correlates with, and is only slightly lower (approximately 15 – 35 %) than, that of their mother following ingestion of a 3 mg dose.

Biotransformation
Melatonin is mainly metabolised in the liver. Experimental data suggests that the cytochrome P450 enzymes CYP1A1 and CYP1A2 are primarily responsible for the metabolism of melatonin, with CYP2C19 of minor importance. Melatonin is primarily metabolised to 6-hydroxymelatonin (constituting approximately 80 – 90 % of melatonin metabolites recovered in the urine). N-acetylserotonin appears to be the primary minor metabolite (constituting approximately 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 (ca. 70 %) and glucuronide conjugation (ca. 30 %) prior to excretion.

Elimination
Plasma elimination half-life ($t_{½}$) is approximately 45 minutes (normal range about 30 – 60 minutes) in healthy adults. Melatonin metabolites are mainly eliminated via the urine, around 90 % as sulphate and glucuronide conjugates of 6-hydroxymelatonin. Less than 1 % of a melatonin dose is excreted unchanged in the 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 t_{max} and plasma $t_{½}$ remain constant.

Gender

Limited data suggests 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
Elderly
The 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 ($t_{½}$) 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 the daytime endogenous blood melatonin concentration is markedly elevated in patients with liver cirrhosis, probably due to reduced clearance (metabolism) of melatonin.
Serum $t_{½}$ 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, repeated dose toxicity, 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 are uncertain.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline (E460)
Maltodextrin
Silica, colloidal anhydrous (E551)
Magnesium stearate (E470b)
Croscarmellose sodium (E468)
Hypromellose (E464)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original container in order to protect from light and moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

HDPE tablet container (white polyethylene bottle) with HPDE/LDPE closure containing dessicant.

Pack size
30 film-coated tablets.

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

Orifarm Generics A/S
Energivej 15
5260 Odense S
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

RVG 125769

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 20. oktober 2020

10. DATE OF REVISION OF THE TEXT

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