Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Melatonin Pharma Nord 3 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 3 mg melatonin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet). Round, biconvex, clear-coated, white to off-white tablet of 7.5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term treatment of jet-lag in adults.

4.2 Posology and method of administration

Posology
The standard dose is 3 mg (1 tablet) daily for a maximum of 5 days. The dose may be increased to 6 mg (2 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 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 reaction, on re-synchronisation following jet-lag, Melatonin Pharma Nord 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 Melatonin Pharma Nord.

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 Melatonin Pharma Nord.

Melatonin Pharma Nord 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 dose recommendations for elderly persons are provided (see section 5.2).

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

Hepatic impairment
There is no experience regarding the use of Melatonin Pharma Nord in patients with hepatic impairment. Limited data indicate thatplasma clearance of melatonin is significantly reduced in patients with liver cirrhosis. Melatonin is not recommended inpatients with hepatic impairment (see section 5.2).

Impaired glucose tolerance
As intake of melatonin with carbohydrate-rich meals may impair blood glucose control for several hours (see section 4.4), it is recommended that Melatonin Pharma Nord is taken at least 3 h after intake of a meal by persons with significantly impaired glucose tolerance or diabetes.

Paediatric population
The safety and efficacy of Melatonin Pharma Nord for the short-term treatment of jet-lag in children and adolescents aged 0 to 18 years have not been established. Melatonin Pharma Nord should not be used for the treatment of jet-lag in children and adolescents aged 0 to 18 years because of safety and efficacy concerns (see sections 4.4 and 5.1).

Method of administration
Oral use.
Tablets should be swallowed whole with fluid.

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. Melatonin should be used with caution if the effects of drowsiness are likely to be associated with a risk to 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 melatonin . 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. Melatonin 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. Melatonin Pharma Nord 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. Melatonin is not recommended for use in patients suffering from severe renal impairment or moderate or severe hepatic impairment.

Cardiovascular conditions
There are limited data that melatonin may cause adverse effects on blood pressure and heart rate in populations with cardiovascular conditions and concurrent antihypertensive medications. It is unclear whether these adverse effects are attributable to melatonin itself or to melatonin-drug interactions. Melatonin is not recommended for use in patients with cardiovascular conditions and concurrent antihypertensive medication (see section 4.5).

Paediatric population
The safety and efficacy of melatonin for the short-term treatment of jet-lag in children and adolescents aged 0 to 18 years have not been established. Melatonin is therefore not recommended for the treatment of jet-lag in children and adolescents (see section 5.1).

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

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 (see section 5.2). 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 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 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 reverse the beneficial effects of antihypertensive medicinal products and increase blood pressure and heart-rate in hypertensive patients treated with such, with especial concern for calcium channel blockers (such as nifedipin).
- Melatonin may affect the anticoagulation activity of warfarin.
- 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).

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 from 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).
Melatonin Pharma Nord is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
There is insufficient information on the excretion of melatonin / metabolites in human milk. Endogenous melatonin is excreted in human milk.
Available pharmacodynamic / toxicological data in animals have shown excretion of melatonin / metabolites in milk (for details see 5.3).
A risk to the newborns/infants cannot be excluded.
Melatonin Pharma Nord 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).
Melatonin Pharma Nord 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 Melatonin Pharma Nord 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 summary of 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 estimated from the available data)
Blood and lymphatic system disorders				leucopenia, thrombocytopenia	
Immune system disorders					hypersensitivity reaction
Metabolism and nutrition disorders				hypertriglyceridaemia	hyperglycaemia
Psychiatric disorders			irritability, nervousness, restlessness, abnormal dreams, anxiety	mood altered, aggressive behaviour, disorientation, libido increased	
Nervous system disorders		headache, somnolence	dizziness	syncope, memory impairment, restless legs syndrome, paraesthesia	
Eye disorders				visual acuity reduced, vision blurred, lacrimation increased	
Cardiac disorders				palpitations	
Vascular disorders			hypertension	hot flushes	
Gastrointestinal disorders			abdominal pain, upper abdominal pain, dyspepsia, oral ulceration, dry mouth, nausea	vomiting, flatulence, salivary hypersecretion, halitosis, gastritis	
Skin and subcutaneous tissue disorders			pruritus, rash, dry skin	nail disorder	tongue oedema, oral mucosa swollen
Musculoskeletal and connective tissue disorders				arthritis, muscle spasms	
Renal and urinary disorders			glycosuria, proteinuria	polyuria, haematuria	
Reproductive system and breast disorders				priapism, prostatitis	galactorrhoea
General disorders and administration site conditions			chest pain, malaise	thirst	

Investigations			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 HPRA Pharmacovigilance Website: www.hpra.ie.

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 to 6,600 mg) for several weeks.
General supportive measures should be employed.
Clearance of the active substance is expected within 12 hours of ingestion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, 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 is 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 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 et al. 1989, BMJ. 298: 705-707.; and Petrie et al. 1993, Biol. Psychiatry 33: 526-530.).
Due to the potential for incorrectly timed intake of melatonin to have no effect, or to cause an adverse reaction, 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 to treat jet-lag in children and adolescents aged 0 to 18 years have not been established. Melatonin is therefore not recommended for the treatment of jet-lag in children and adolescents aged 0 to 18 years. 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. 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 ~ 3,400 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 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 Melatonin Pharma Nord, 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 % to 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 % to 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 % to 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 ($t_{½}$) 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/non-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 mg to 6 mg whereas t_{max} and plasma $t_{½}$ 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
Elderly
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 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 to 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 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 in non-clinical studies 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 palm 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 palm squirrel are seasonal breeders, the implications of these findings for humans are uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Magnesium stearate
Colloid silica, anhydrous
Maltodextrin
Microcrystalline cellulose
Croscarmellose sodium

Film-coating
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

10 or 30 film-coated tablets in transparent PVC/PVDC//Alu blister and carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Pharma Nord ApS
Tinglykke 4-6
DK-6500 Vojens
Denmark

8 MARKETING AUTHORISATION NUMBER

PA1242/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th November 2019
Date of last renewal: 30th July 2023

10 DATE OF REVISION OF THE TEXT

May 2023