SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Syncrodin® 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. Round, biconvex, clear-coated, white to off-white tablet of size 7.5 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Syncrodin® 3 mg film-coated tablets is indicated for:

I. Short-term treatment of jet-lag in adults.

II. Treatment of delayed sleep wake phase disorder (DSWPD) in children and adolescents aged 6 to 17 years and adults up to 25 years of age, where sleep hygiene measures have been insufficient.

III. Treatment of insomnia in children and adolescents aged 6 to 17 years with attention deficit hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient.

IV. Treatment of insomnia (prolonged sleep onset) in children and adolescents aged 6 to 17 years with autism spectrum disorder (ASD), where sleep hygiene measures have been insufficient.

4.2 Posology and method of administration

Posology

- *Adults with jet-lag*

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 effect, on re-synchronisation following jet-lag, Syncrodin® tablets 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 Syncrodin® 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 Syncrodin®.

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 Syncrodin®.

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

Paediatric population

The safety and efficacy of melatonin in children and adolescents less than 18 years in jet-lag has not been established.

- *Delayed sleep wake phase disorder (DSWPD) in children and adolescents aged 6 to 17 years and adults up to 25 years of age, where sleep hygiene measures have been insufficient.*

Diagnosis and treatment of DSWPD should be made and initiated by physicians experienced in DSWPD and/or paediatric sleep medicine.

The recommended starting dose is 1 to 2 mg per day given 1 to 2 hours before the fixed desired bedtime or at the time advised by the treating physician.

The dose of melatonin should be adjusted individually until effective up to a maximum of 5 mg per day, independent of age. The lowest effective dose should be sought and taken for the shortest period. Syncrodin® is suitable only when the lowest effective dose has been established to be 3 mg. Other formulations and strengths suitable for paediatric patients may also be available on the market.

After 6 weeks of treatment, the physician should evaluate the effect of treatment and consider stopping treatment if no clinically relevant treatment effect is seen. In patients with significant continuing daytime sleepiness or misaligned circadian rhythm the possibility of high residual melatonin in the morning should be considered. In these cases, Syncrodin® can be stopped and restarted at a lower dose. The dose that adequately alleviates symptoms should be taken for the shortest period.

There is insufficient safety data to support long term use of melatonin in children approaching puberty. After the achievement of advanced sleep-wake phase for 6 weeks, treatment should be stopped to evaluate if the patient can independently maintain an advanced sleep-wake schedule. If discontinuation of melatonin leads to clinical relapse, melatonin can be reinstated and continued. The patient should be monitored at regular intervals to check that Syncrodin® is still the most appropriate treatment. During ongoing treatment, especially if the treatment effect is uncertain, discontinuation attempts should take place regularly at the discretion of the treating physician. Limited data are available for up to 3 years of treatment.

Children under 6 years of age

Syncrodin® is not recommended for children under 6 years of age.

Adults over 25 years of age

In adults whose symptoms persist past the age of 25 and who have shown clear benefit from treatment, it may be appropriate to continue treatment. However, initiation of treatment in adults over 25 years of age is not appropriate.

- *Insomnia in children and adolescents aged 6 to 17 years with attention deficit hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient.*

Diagnosis and treatment of insomnia associated with ADHD should be made and initiated by physicians experienced in ADHD and/or paediatric sleep medicine.

Syncrodin® is taken 30 to 60 minutes before bedtime.

Syncrodin® is suitable only when the lowest effective dose has been established to be 3 mg. If a patient requires other doses, then alternate formulations should be used. Maximum dose: 5 mg.

The dose of melatonin should be adjusted individually until effective up to a maximum of 5 mg per day, independent of age. The lowest effective dose should be sought. Other formulations and strengths suitable for paediatric patients may also be available on the market.

Within the first 3 months of treatment, the physician should evaluate the effect of treatment and consider stopping treatment if no clinically relevant treatment effect is seen. The patient should be monitored at regular intervals as determined by an appropriate prescriber to check that Syncrodin® is still the most appropriate treatment. Limited data are available for up to 3 years of treatment.

During ongoing treatment discontinuation attempts should be attempted regularly, e. g. once per year and treatment discontinued if it is not effective.

If the sleep disorder has started during treatment with medicinal products for ADHD, dose adjustment or switching to another product should be considered. If significant

problems are seen in sleep maintenance or early morning waking, an alternative formulation of melatonin should be considered.

Children under 6 years of age

Syncrodin® is not recommended for children under 6 years of age.

- *Insomnia (prolonged sleep onset) in children and adolescents aged 6 to 17 years with autism spectrum disorder (ASD), where sleep hygiene measures have been insufficient.*

Diagnosis and treatment of insomnia (prolonged sleep onset) associated with ASD should be made and initiated by physicians experienced in ASD and/or paediatric sleep medicine.

The recommended starting dose is 1 to 2 mg. Syncrodin® is suitable when the effective dose for the patient is 3 mg or multiples of 3 mg. If a patient requires other doses, then alternate formulations should be used. Syncrodin® should be given 30 to 60 minutes before bedtime. If an inadequate response has been observed, the dose should be increased under the supervision of a physician to 5 mg, with a maximal dose of 10 mg. The lowest effective dose should be sought. Other formulations and strengths suitable for paediatric patients may also be available on the market.

Within the first 3 months of treatment, the physician should evaluate the effect of treatment and consider stopping treatment if no clinically relevant treatment effect is seen. If a lower treatment effect is seen after titration to a higher dose, the prescriber should first consider a down-titration to a lower dose before deciding on a complete discontinuation of treatment. The patient should be monitored at regular intervals as determined by an appropriate prescriber to check that Syncrodin® is still the most appropriate treatment. Parents should be encouraged to monitor sleep carefully pre, during and post treatment breaks using paper or online sleep diaries. During ongoing treatment discontinuation attempts should be attempted regularly, e.g. once per year and treatment discontinued if it is not effective. If benefits are maintained there should still be a 5-day break once a year to ensure that the medication is still required. Limited data are available for up to 3 years of treatment.

Children under 6 years of age

Syncrodin® is not recommended for children under 6 years of age.

Special populations

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 Syncrodin® in patients with renal impairment. Caution should be exercised if Syncrodin® is used by patients with renal impairment. Syncrodin® is not recommended for patients with severe renal impairment (see sections 4.4 and 5.2).

Hepatic impairment

There is no experience regarding the use of Syncrodin® in patients with hepatic impairment. Limited data indicate that plasma clearance of melatonin is significantly reduced in patients with liver cirrhosis. Syncrodin® is not recommended in patients with moderate or severe hepatic impairment (see sections 4.4 and 5.2).

Children under 6 years of age

Syncrodin® is not recommended for children under 6 years of age.

Method of administration

Oral use.
Tablets should be swallowed whole with fluid. Tablets must not be broken, crushed or chewed.

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

Epilepsy

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

Immunological diseases

Occasional case reports have described exacerbation of an autoimmune disease in patients taking melatonin. Syncrodin® is not recommended in patients with autoimmune diseases.

Diabetes/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. Syncrodin® 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 people with significantly impaired glucose tolerance or diabetes.

Renal and hepatic impairment

Only limited data are available on the safety and efficacy of melatonin in patients with renal impairment or hepatic impairment. Syncrodin® is not recommended for use in patients suffering from severe renal impairment or moderate or severe hepatic impairment (see sections 4.2 and 5.2).

Paediatric population

There is insufficient data to analyse the impact of long-term exposure to melatonin in children and adolescents on the sexual maturation of this population. There are theoretical risks based on biological effects of melatonin, e. g. immunological regulation, effects on the threshold for seizures and endocrinological effects, which could affect puberty development and fertility, respectively. Therefore, treatment should be taken for the shortest period and evaluated on a regular basis as determined by the treating physician to check that Syncrodin® is still the most appropriate treatment.

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 active substance 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 active substance increases melatonin levels by inhibiting its metabolism.
- Caution is indicated in patients taking cimetidine, since this active substance 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

Benzodiazepine-related hypnotics
- Melatonin may enhance the sedative effect of benzodiazepines (e. g., midazolam, temazepam) and non-benzodiazepine hypnotics (e. g., zaleplon, zolpidem, zopiclone). Concomitant treatment with melatonin should be avoided.

Alcohol
- Alcohol should not be used concomitantly with melatonin since it may reduce the effect of melatonin on sleep.

Nifedipine
- Melatonin may reduce the hypotensive effect of nifedipine. Caution must be taken during the concomitant use of melatonin, and adjustment of the nifedipine dose may be needed. As it is not known if this is a class effect, caution should be exercised when combining melatonin with other calcium channel blockers.

Warfarin
- It has been reported in case studies that the concomitant use of melatonin and vitamin K antagonists such as warfarin can lead to either increased or decreased prothrombin levels, and a study has shown decreased levels of factor VIII and fibrinogen. The combination of warfarin and other vitamin K antagonists with melatonin may require dose adjustment of the anticoagulant medicinal product and should be avoided.

NSAIDs
- Prostaglandin synthesis inhibitors (NSAIDs) such as acetylsalicylic acid and ibuprofen, taken in the evening, may suppress the night-time release of endogenous melatonin levels. If possible, administration of NSAIDs should be avoided in the evening.

Beta-blockers
- Beta-blockers may suppress the night-time release of endogenous melatonin and should therefore be administered in the morning.

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). Syncrodin® 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 breast-fed new-born, infant and child cannot be excluded. Syncrodin® 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). Syncrodin® 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 Syncrodin® 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 Syncrodin® 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)

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	

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)
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	

Paediatric population

A low frequency of mild adverse reactions has been reported in the paediatric population. The number of adverse reactions in patients given melatonin or placebo is not significantly different. The most common adverse reactions include headache, hyperactivity, dizziness and abdominal pain. No serious adverse reactions have been reported.

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 Yellow Card Scheme at 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 reported signs and symptoms of overdose with oral melatonin.

Daily ingestion of melatonin, in the dose range 20 to 300 mg, for time periods of up to 2 years, have been reported in the literature, without any clinically significant adverse reactions. One dose of 250 mg taken 4 times daily over a period of 25 to 30 days has been reported to cause only drowsiness/sleepiness.

Also, in several cases of reported overdosing, mildly to moderately severe somnolence was the most reported adverse reaction. 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. Due to the short half-life of melatonin, clearance of the active substance is expected within 12 hours of ingestion. A physician should assess if conventional overdose measures

should be taken. General supportive measures should be employed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Chemical substance: melatonin, Anatomical main group: nervous system, Therapeutic group: psycholeptics, Pharmacological sub-group: hypnotics and sedatives, Chemical sub-group: melatonin receptor agonists, ATC code: N05CH01.

Melatonin is a hormone and endogenous antioxidant produced by the pineal gland. Melatonin is synthesized from an essential amino acid, tryptophan and is structurally similar to serotonin.
Melatonin secretion increases shortly after dark, reaching its peak between 2 am and 4 am and decreases during the latter half of the night. Melatonin acts as a chronobiotic and is involved in controlling the circadian rhythm and adaptation to the light-dark cycle. Melatonin helps to regulate the body's day and night rhythm and is associated with a sedative effect and an increased propensity for sleep (rapid onset of sleep). In addition to the pineal gland, some melatonin is synthesized in the retina, bone marrow, gastrointestinal tract, and bile. Exogenous melatonin can change the timing of some overt rhythms such as sleep, core body temperature and endogenous melatonin.

Mechanism of action

Melatonin exerts its effects through two primary pathways, namely a receptor-mediated pathway and a receptor-independent pathway. The pharmacologic mechanism of action of melatonin is believed to be based on its interactions with MT1, MT2, and MT3 receptors, given that these receptors, specifically MT1 (high affinity) and MT2 (low affinity), are involved in the regulation of sleep (hypnotic effect) and circadian rhythms in general (chronobiotic effect).

Pharmacodynamic effects

The primary function of melatonin is to synchronise the circadian rhythm of the body, particularly relating to sleep. The circadian master clock is located within the suprachiasmatic nucleus (SCN) of the hypothalamus, which controls the synthesis and release of melatonin. Melatonin in turn distributes circadian cues generated by the SCN to tissues containing melatonin receptors. Due to the expression of melatonin receptors in the SCN, melatonin is able to effect feedback control of the SCN master clock. Thus, administration of exogenous melatonin can synchronize the SCN clock when out of phase, advancing sleep onset and reduces sleep onset latency. Several clinical studies have linked sleep promotion following administration of exogenous melatonin with increased theta-alpha activity quantified via electroencephalography. There is no evidence that the basis for this physiological action is different in children compared to adults.

Clinical efficacy and safety

Adults with jet-lag

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.). 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.

Delayed sleep wake phase disorder (DSWPD) in children, adolescents aged 6 to 17 years and adults up to 25 years of age

Eleven randomised controlled trials have been carried out in which supplementary melatonin was administered orally to improve sleep onset insomnia in children, adolescents and adults associated with delayed sleep-wake phase disorder. Each of the studies comprised individuals who had been clinically diagnosed with DSWPD, but who otherwise did not suffer from neurological disorders such as ASD or ADHD; the total number of individuals in these studies was 818, covering the age range 7 to 80 years. Nine of these studies used an immediate release form of melatonin with daily dosages ranging from 0.5 to 5 mg over a period typically of 4 weeks. For the two studies using a controlled-release melatonin formulation of 2 mg, 40% of the total dose (0.8 mg) would be released immediately. All studies reported significant improvements with the time taken to sleep onset reduced by 45 minutes. A further eight clinical studies (non-randomised) reported significant improvements in sleep onset delay in adults and children and adolescents aged 6 to 17 years. These studies demonstrated that melatonin was generally well-tolerated, with only mild side effects observed and no serious adverse events reported.

Insomnia in children and adolescents aged 6 to 17 years with ADHD

Evidence supporting the use of supplemental melatonin for treating insomnia in children and adolescents with ADHD is based on a randomised controlled trial comprising 105 individuals aged 6 to 12 years. The study utilised an immediate release melatonin formulation, with daily dosages ranging from 3 to 6 mg over a 4-week period. There was a significant improvement in sleep onset delay of 38 minutes. Another clinical trial in a sample of 27 children aged 6 to 14 years showed that combining sleep hygiene and melatonin resulted in significant improvements with the time taken to sleep onset reduced by 60 minutes. These studies demonstrated that melatonin was generally well-tolerated, with only mild side effects observed and no serious adverse events were reported.

Insomnia (prolonged sleep onset) in children and adolescents aged 6 to 17 years with ASD

The efficacy and safety of melatonin for treating insomnia (prolonged sleep onset) in children and adolescents aged 6 to 17 years with ASD have been assessed in two randomised controlled trials comprising a total of 256 individuals aged 3 to 15 years. Both studies utilised an immediate release melatonin formulation, with daily dosages ranging from 0.5 to 12 mg over a period of 2 to 12 weeks. Both studies reported significant improvements with the time taken to sleep onset reduced by 28 and 37 minutes, respectively. Other clinical reviews and UK clinical audits of the use of immediate release melatonin in children and adolescents, including those with ASD, also reported similar significant improvements in sleep onset delay. These studies demonstrated that melatonin was generally well-tolerated, with only mild side effects observed and no serious adverse events reported.

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. The main difference between children and adults in the pharmacokinetics of exogenous melatonin is the increased rate of clearance in younger (pre-pubertal) children, resulting from increased enzymic activity of CYP1A2 (the principal metaboliser of melatonin) in the liver; this in turn may require a higher dose of melatonin to induce sleep than would be required in adults. There is no physiological rationale why intrinsic or extrinsic factors potentially affecting melatonin pharmacokinetics reported in adults could be different in children, and this is reflected in the relevant sections of the SmPC below.

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 Syncrodin®; however, it is recommended that food is not consumed approximately 2 h before and 2 h after intake of melatonin. People with significantly impaired glucose tolerance or diabetes ideally should wait at least 3 hours after a meal before taking Syncrodin®.

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 to 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 (see section 4.2).

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 (see sections 4.2 and 4.4).

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 to increase in patients with severe renal impairment (see sections 4.2 and 4.4).

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. Onset of sexual maturation in animals such as 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. Animal studies have found that melatonin affects the onset of sexual development. As the studied animals were seasonal breeders, the implications of these findings for humans are uncertain and theoretical.

There is no evidence for such effects in humans (see section 5.1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Magnesium stearate (E470b)
Colloid silica, anhydrous (E551)
Maltodextrin
Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)

Film-coating

Hypromellose (E464)

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

5, 7, 10, 14, 20, 28, or 30 film-coated tablets in transparent PVC/PVdC//Alu blister and carton.
Each blister contains 5, 7, 10, 14, 20, or 30 tablets.

Not all pack sizes may be marketed.

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

Pharma Nord ApS
Tinglykke 4-6
6500 Vojens
Denmark

8 MARKETING AUTHORISATION NUMBER(S)

PL 20243/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/07/2022

10 DATE OF REVISION OF THE TEXT

29/04/2025