COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Melatonine Pharma Nord 3 mg film-coated tablets

(melatonin)

NL/H/4030/001/DC

Date: 19 December 2018

This module reflects the scientific discussion for the approval of Melatonine Pharma Nord 3 mg film-coated tablets. The procedure was finalised at 30 July 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AEs	Adverse Events
API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MRHD	Maximum Recommended Human Dose
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PT	Pars Tuberalis
RH	Relative Humidity
RMP	Risk Management Plan
SCN	Suprachiasmatic Nucleus
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Melatonine Pharma Nord 3 mg film-coated tablets, from Pharma Nord ApS.

The product is indicated for the short-term treatment of jet-lag in adults.

Melatonin is a hormone produced by the pineal gland during the night in response to light/dark information received by the retina. The plasma concentration of melatonin exhibits a circadian pattern, rising in the evening with dim light (Dim Light Melatonin Onset (DLMO)), increases progressively to reach maximal values in the middle of the night and then decreases progressively to reach minimal values in the morning. This endogenous melatonin rhythm may be disturbed by flying over several time zones. Exogenous melatonin may help re-entrain the natural cycle.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of melatonin. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the Marketing Authorisation Holder (MAH) can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. “Medicinal use” does not exclusively mean “use as an authorised medicinal product’’, so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the MAH should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

The concerned member state (CMS) involved in this procedure was Hungary.
The active substance melatonin has been used in the community (specifically Hungary and Denmark) for more than 10 years for the indication jet leg. Furthermore, an EU organisation, the European Food Safety Authority (EFSA), published a Scientific Opinion supporting the use of melatonin for this indication, although this publication was less than 10 years ago (i.e. in 2010).

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The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, a bibliographical application.

II. QUALITY ASPECTS

II.1 Introduction

Melatonine Pharma Nord is a round, biconvex, clear-coated, white to off-white film-coated tablet and contains 3 mg melatonin.

The film-coated tablets are packed in coated tablets in transparent PVC/PVDC//Alu blisters.

The excipients are:
Tablet core – magnesium stearate, anhydrous colloid silica, maltodextrin, microcrystalline cellulose and croscarmellose sodium
Film-coating - hypromellose

II.2 Drug Substance

The active substance is melatonin, an established active substance described in the British Pharmacopoeia (BP) and United Stated Pharmacopeia (USP). It is not described in the European Pharmacopeoia (Ph. Eur.). Melatonin is a white to off-white powder and slightly soluble in water and sparingly soluble across the pH range 1.2 to 6.8. The drug substance is not chiral and obtained in one crystalline form only.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the MAH or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

<u>Manufacturing process</u>
The synthetic route consist of two chemical steps and three purification steps. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and has been established in-house. It includes tests for description, identification, melting point, loss on drying, water content, sulphated ash, related substances, assay and microbial purity. The specification of the MAH is acceptable in view of European guidance and requirements. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for nine full scale batches stored at 25°C/60% RH (12 to 60 months), 30°C/65%RH (12 months) and 40°C/75% RH (6 months). No significant changes or trends have been observed. The claimed re-test period of 60 months has been justified when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. The product applied for has been tested for dissolution in line with relevant EU guidance on bioequivalence. The results show that for all products (test and reference) 85% dissolved in 15 minutes.

The application corresponds to a well-established use application. Information from literature is limited. The products described concern immediate release products, as is the same for the proposed product. With regard to dissolution (as per Ph.Eur.) and disintegration (as per Ph.Eur.) characteristics, the tablet complies to the Ph. Eur. as defined for an immediate release tablet. Taken into account the above dissolution studies it is concluded that the MAH made sufficiently plausible that the compositions and release characteristics (by means of dissolution data) of the product(s) used in the literature studies are comparable to those of the proposed product.

Overall, the pharmaceutical development has been adequately performed. Sufficient information has been provided with respect to the overall development of the product.

Manufacturing process

The manufacturing process involves direct compression. The drug substance and excipients are mixed in a specific order and the final blend is compressed and coated. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients
All excipients and components of excipients comply with the Ph.Eur. The specifications are acceptable, relevant functional related characteristics are added to the specifications if applicable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance and size, average weight, uniformity of mass and dosage units, disintegration time, dissolution, identification, assay, related substances, and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for five full scale batches stored at 25°C/60% RH (24-36 months), 30°C/65%RH or 30°C/75% RH (12-24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial packaging. The trends and changes remain within the specification. A photostability study showed that the product is sensitive to light. On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are “This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Melatonine Pharma Nord has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

No non-clinical studies have been performed by the MAH. Extensive preclinical tests concerning pharmacology and toxicology have been described in the literature. The MAH

selected the most relevant studies/reviews which are used in the non-clinical overview to support this application. Since melatonin can be regarded as a well known substance it is agreed that a non-clinical overview based on literature review is appropriate and no additional studies are required from the MAH.

III.2 Pharmacology

In vitro studies and mechanism of action

There are two pharmacologically identified subtypes of melatonin receptors, MT1 and MT2. Two human MT1-like receptors, Mel1a and Mel1b, have been cloned. They are both high affinity, G protein coupled receptors with 60% homology at the amino acid level. When human Mel1a was expressed in Chinese Hamster Ovary cells, melatonin was found to inhibit forskolin-induced cAMP formation in a concentration-dependent and biphasic manner, which indicates that receptor signalling involves inhibition of cAMP and that melatonin binds to high and super high affinity states of the receptor. Mel1a receptors or Mel1a mRNA have been localised in the suprachiasmatic nucleus (SCN) of human, hamster and rat. These receptors mediate most probably the circadian effects of melatonin. Mel1b receptors are expressed in the retina and the brain. These receptors may mediate the effects of melatonin on retinal physiology including photo pigment disc shedding and phagocytosis.

The density of melatonin binding sites was determined in the rat pars tuberalis (PT) and SCN. The results indicated that the daily variations in plasma melatonin concentrations is involved in the regulation of the density of melatonin binding sites both in PT and SCN.

A clear diurnal expression of melatonin receptor mt1 mRNA in the rat PT was demonstrated in a study, which found a high level of mt1 mRNA at the end of the night and a low level during the day and the early night.

In vivo studies

There are limited public records of non-clinical *in vivo* studies investigating the primary pharmacology of melatonin in relation to regulation of the circadian rhythm and other physiological effects relevant to short-term treatment of jet lag. Non-clinical data obtained using nocturnal animals, such as mice and rats, may be difficult to interpret and relate to diurnal animals and humans.

In rats with free-running circadian rhythms, oral and subcutaneous administration of melatonin resulted in a stable diurnal rhythm. When melatonin was given intraperitoneally to rats, a significant decrease in core body temperature was observed for at least the following 3 hours. Whether melatonin has sleep-inducing and sleep-prolonging effects in rats remains controversial.

In a study using macaques, a physiological dose of melatonin administered orally 2 hours before lights-off time promoted significant earlier sleep onset. As the sleep offset time was not affected, the total sleep period increased. Long-term melatonin treatment did not result in development of tolerance or sensitisation to melatonin effects on sleep.

Efficacy of melatonin is based mainly on clinical information.

Safety pharmacology

Cardiovascular system

Melatonin showed a contractile effect of melatonin on rat cerebral arteries. In contrast to this cerebral vasoconstriction, an *in vivo* study of rats under urethane anaesthesia showed that melatonin decreases brain serotonin release and results in sympathetic inhibition or parasympathetic stimulation which leads to hypotension and bradycardia in rats. However, the relevance of these findings to potential adverse cardiovascular effects of clinical use of melatonin is limited.

Intravenously administered melatonin had no effect on the blood pressure in the cat, and melatonin did not alter the contractile force or electrocardiogram of the dog.

In baboons, melatonin caused a statistically significant increase of the cardiac output and ventricular ejection associated to a reduction in heart rate at 17 times the maximum recommended human dose (MRHD).

Nervous system

In mice, the Irwin test showed that melatonin doses 460 times human exposure had no behavioural effects. Repeated daily administration in mice at 145 times MRHD significantly reversed the increase in immobility period that was observed on chronic exposure to the swimming test, indicating an anti-depressant activity on chronic forced-swim induced despair behaviour.

Pharmacodynamic drug interactions

As both melatonin and benzodiazepines bind GABA-A receptors, there is a potential for pharmacodynamic interaction with benzodiazepines. An *in vitro* study using rat brain tissue found that melatonin inhibited binding of the benzodiazepine diazepam to purified rat brain synaptosomal. *In vivo*, the combination of melatonin plus diazepam (but not either drug alone) was found to increase the duration of immobility in the mouse tail suspension test. However, the dose of melatonin used is extremely high.

III.3 Pharmacokinetics

Absorption, Distribution, Metabolism and Excretion

Melatonin is rapidly absorbed from the gastrointestinal tract. There is limited evidence of nonlinear pharmacokinetics of orally administered melatonin in dogs and monkeys, whereas oral data from humans indicate linearity. Particularly relevant to the MAH's orally administered product is the high extent of first-pass metabolism in humans resulting in low bioavailability values ranging 10- 56%. The distribution of melatonin among tissues is relatively fast with an elimination half life from serum of ~20 minutes in rats and longer elimination half-life in primates than in rodents. Studies in rats showed that the liver is a main site of very rapid melatonin metabolism. Limited published data indicate that <1% of exogenous melatonin is excreted unchanged in the urine.

III.4 Toxicology

Single dose toxicity
Melatonin has a very low acute toxicity on administration of single oral doses. LD50 values of ≥930 mg/kg and 3200 mg/kg have been reported for the mouse and rat, respectively, which is tens of thousands times more than the MRHD.

Repeat-dose toxicity
The effect of repeated dose exposure to melatonin has been investigated in mouse and rat studies mostly addressing survival. Several studies found evidence of prolonged survival of mice or rats subjected to long-term oral treatment with melatonin in moderate amounts (though several fold higher than the MRHD). However, systematic safety studies have not been performed, and data from non-rodents are not available.

Genotoxicity
A full battery of genotoxicity tests have been performed with melatonin. Although the individual studies were generally not conducted specifically according to ICH guidelines, and GLP status was not reported, they consistently found no evidence that melatonin is genotoxic (neither mutagenic nor clastogenic). A single study group reported that in several test systems very high *in vitro* exposures induced DNA adducts of uncertain consequence for carcinogenic risk.

Carcinogenicity
Available information is considered to indicate that additional studies are unwarranted. Relevant information includes lack of genotoxicity following testing in the required non-clinical systems, no clear evidence of carcinogenicity in animal studies, and lack of evidence of carcinogenicity in epidemiological data. In addition, it is also considered relevant that numerous *in vitro* and *in vivo* nonclinical studies, and *ex vivo* clinical studies have found melatonin to reduce the potency of known mutagens and carcinogens.

Reproductive and developmental toxicity
Fertility and early embryonic development
Several rat studies showed that sexual maturation was delayed, however not prevented, in young female and male rats after s.c. administration of melatonin for periods of several days to several weeks.
However, in humans sexual maturation and the reproductive cycle are not dependent on season (photoperiod), which makes it unlikely that melatonin plays a significant role in the development of sexual maturity in humans. Nevertheless, for the current application, melatonin is indicated for persons of 18 years and over, and that its use by women who are pregnant or lactating, or by women and men planning a pregnancy is not recommended.
No adverse effect of melatonin was found on sexual behaviour in two rat studies. Embryonic *in vitro* studies in rat, mouse and pig did not indicate any adverse effect of melatonin on *in vitro* fertilisation and early embryonic development.

Embryo- foetal development
Several studies in mice and rats showed that melatonin had no toxic effect on embryo-foetal development. No maternal deaths occurred. None of the rodent studies found any effect of melatonin on the morphological development of embryos and foetuses in utero.

Prenatal and postnatal development, including maternal function
Published data on potential effects of melatonin on pre- and postnatal development are limited and the implications of these findings for humans are uncertain. However, the non-clinical data indicate that melatonin traverses the placenta and that it is excreted in milk. Thus, melatonin is not recommended to women during pregnancy or lactation.

Local tolerance
No specific studies were found. The current product is intended for the oral route of administration and there is an absence of gastro-intestinal findings in the general toxicology studies.

Studies on impurities
Available guidance regarding genotoxic impurities was applied to justify that the limit proposed in the active pharmaceutical ingredient (API). The ASMF holder has developed and validated a method to detect these impurities in the API. Analysis of three batches of the melatonin API found the impurities to be present below the acceptable limit in all batches.

III.5 Ecotoxicity/environmental risk assessment (ERA)

The MAH provided phase I data. However, there are sufficient arguments to justify the absence of ERA studies. Melatonin is a biogenic amine; it is produced and excreted by animals and plants; in this context the contribution to environmental exposure from human use is considered non-significant. In addition, the limited environmental data as provided by the MAH do not indicate a specific hazard. Therefore, melatonin is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

The application for this product is based on well-established use. This is endorsed, since melatonin has been registered for this indication for a long time and the dose is not increased. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

The MAH sufficiently supported each section of pharmacokinetic properties of SmPC. In addition, the MAH has adequately substantiated bridging between their product and the products used in the literature. Melatonin is considered a 'Biopharmaceutics Classification System' -class I drug and neither Melatonin Pharma Nord nor melatonin formulations used in the jet-leg studies contained active excipients that could potentially affect absorption of melatonin. Therefore, considering linear pharmacokinetic of melatonin, similar exposure between the MAH's product and the products used in the literature can be expected. In addition, the MAH has provided comparative dissolution data on the proposed product and the acceptable reference products capsule Handmade 5 mg and Capsule Penn Pharmaceutical 5 mg. The study was performed in pH 1.2, 4.5 and 6.8, using the basket method and RPM of 100, which is the acceptable speed for a basket method). The volume used (500 ml) is justified (usual is 900 to 1000 ml). The results of all three products showed that after 15 minutes over 85% was dissolved. The products can be regarded as similar.

Absorption

Oral melatonin is efficiently (almost completely) absorbed from the gastrointestinal tract by first-order kinetics, though bioavailability (F) is low (~ 5%; range in individuals 1 to 56%) due primarily to extensive first-pass metabolism. A 3-6 mg dose of IR melatonin results in a peak in plasma melatonin concentration (T_{max}) ~50 minutes (normal range ~25- 75 minutes) after ingestion. A 3 mg dose can be expected to result in a C_{max} of ~3400 pg/mL, which is ~60-times the peak nocturnal (endogenous) plasma melatonin Cmax, though both values are subject to considerable inter-individual variation. C_{max} and AUC (area under the concentration-time curve) are linear for oral melatonin doses in the range 0.1 to at least 5 mg, whereas T_{max} (and plasma elimination half-life ($T_{½}$)) are constant. Limited data suggest that ingestion of melatonin with food can increase absorption (C_{max} and AUC are increased) though with limited effect on T_{max}.

Distribution

Plasma protein binding is in the range 50-60%; binding is primarily to albumin with limited binding to other plasma proteins. Melatonin is not strongly or extensively bound to plasma proteins, therefore significant effects of protein binding on melatonin pharmacokinetics (or drug interactions based on plasma protein binding) are not expected.

Metabolism

The cytochrome P450 system enzymes CYP1A1 and CYP1A2 are primarily responsible for metabolism of melatonin, with the liver the primary site of metabolism. The contribution of extra-hepatic metabolism is unclear but is minor. 6-hydroxymelatonin is the primary metabolite (~80-90% of melatonin metabolites recovered in the urine). Its formation is rapid, with plasma 6-hydroxymelatonin level rising within minutes of melatonin entering the systemic circulation. N-acetylserotonin, conjugated with glucuronide or sulphate, appears to be the primary minor metabolite. 5-methoxytryptamine, 2-hydroxymelatonin, and kynuramine derivatives are other more minor metabolites.

Excretion

Excretion of melatonin metabolites, and a small quantity of melatonin (< 1%), occurs predominantly via the kidneys; faecal excretion of melatonin and its metabolites following ingestion of typical therapeutic doses of melatonin appears negligible. 6-hydroxymelatonin is excreted as its sulphate (~ 70%) and glucuronide (~ 30%) conjugates. T½ in healthy adults (including the elderly) is ~ 45 minutes (normal range ~ 30 – 60 minutes) and is essentially constant at oral doses up to 100 mg. T½ follows first-order (biphasic) elimination kinetics, and is independent of dose and route of administration.

Special populations

The pharmacokinetics of oral IR melatonin in the range 0.3 – 6 mg is generally comparable in younger and older adults, though the range of values for a given parameter tends to be greater in the elderly. There do not appear to be significant differences in the pharmacokinetics of oral IR melatonin in men and women, though Cmax, AUC and F may be higher in women; no such tendency is evident for T½. Data for the influence of race and genetic factors are limited, but are not considered suggest any major concerns for efficacy or safety. Limited data indicate that hepatic impairment can reduce the clearance of exogenous melatonin, though the data are inadequate to allow correlation between degree of hepatic impairment and impact on clearance. Data regarding the effect of renal impairment on the clearance of exogenous melatonin are not available, though only a very small fraction (less than ~ 1%) of exogenous melatonin is excreted untransformed in urine. However as melatonin metabolites are predominantly excreted in the urine, renal impairment can be expected to reduce their elimination.

Interactions

As melatonin is metabolised mainly by CYP1A isoenzymes there is potential for pharmacokinetics interactions with other drugs for which CYP1A is an important route of metabolism. Drugs that have been found to reduce metabolism of exogenous melatonin – resulting in a clinically significant increase plasma melatonin level – include fluvoxamine, methoxypsoralens, and oestrogens, with caffeine having a lesser effect. Other drugs that, due to their route(s) of metabolism, can also be expected to reduce metabolism of melatonin, but for which no data for exogenous melatonin were identified, include quinolones (such as ciprofloxacin) and cimetidine. Drugs that, due to their capacity to induce cytochrome P450 isoenzymes, can be expected to increase metabolism of melatonin – and thus increase plasma melatonin level – but for which no data for exogenous melatonin were

identified, include carbamazepine and rifampicin. No pharmacokinetic interactions clearly involving drug transporters were identified.

IV.3 Pharmacodynamics

The precise mechanism of action of melatonin is not known, although it seems that MT1 receptors in the SCN and MT2 receptors in the retina and the hypothalamus are involved. Other mechanisms of action, including those that do not involve the MT1 and MT2 receptors, can not be excluded (e.g. serotonin receptors in the SCN).

Altogether, the pharmacodynamic studies presented in this section suggest that exogenous melatonin causes a dose-dependent reduction in core body temperature, which is followed by a dose-dependent (minimal 5-9 mg) reduction in sleep latency (about 10 minutes according to one study). Increase in total sleep time has also been reported in one study.

Secondary pharmacology of melatonin suggest effects on the immune system. These effects may call for caution in using melatonin in immune compromised patients. The company presents published case reports concerning autoimmune reaction in response to treatment with melatonin. Based on this the company proposes a warning text for Section 4.4 of the SmPC indicating that melatonin is not recommended in patients with autoimmune diseases, which is accepted.

In addition, hormonal effects were observed, including enhancement of luteinizing hormone levels in women during the follicular phase of the menstrual cycle, and of cortisol levels in older women, as well as enhancing prolactin secretion, and decreasing plasma progesterone and estradiol levels in healthy women and reducing glucose tolerance and insulin sensitivity. Melatonin may have an effect on fertility in women and men, on pregnancy, and on breast feeding. Although the evidence to supports such effects are sparse, warnings about these effects are included in the relevant SmPC sections and this is agreed to be adequate measures to address these uncertain risks.

Evidence from the literature also suggests that melatonin can increase plasma glucose in healthy persons and that there is a potential for interaction with food. Therefore the company proposes to include a warning indicating that intake of melatonin with carbohydrate-rich meals may impair blood glucose control and should therefore be avoided for 2 hours before and 2 hours after intake of melatonin. This is accepted.

IV.4 Clinical efficacy

Altogether 10 studies are presented in support of the jet lag indication. All studies examined healthy volunteers. Some were accustomed to international flight and had experienced discomfort after an eastward trip. Study participants were recruited from diverse segments of the population such as visitors to a university travel clinic, physicians, university and airport staff, medical personnel, sports officials, scientists and airline cabin crews. Therefore,

the overall study population is considered representative of intercontinental flight passengers. In addition, participant age ranged from the mid twenties to mid sixties in most studies, and reasons for travel included work and leisure.

Studies were generally small, including 10-15 patients per arm (the studies by Arendt' 87, Arendt & Aldhous '88, Petrie'89, Claustrat '92, Petrie '93, Nickelsen '91, Edwards 2000,) 3 studies included around 60 subjects per arm (Suhner '98a, Suhner '98b and Spitzer '99).

The dose range used in the studies was 0.5 mg to 10 mg. However, results of studies with low dose of melatonin (i.e. 0.5 mg and 2 mg in the study by Suhner '98a and 0.5mg in Spitzer '99) suggest that such low doses are not effective. Therefore recommending 3mg with a possibility to increase to 6mg, as in the proposed posology, is supported by the evidence.
Timing of intake, i.e. at habitual bedtime at destination is supported. Individual variations in melatonin metabolism exist, there is no strong basis to recommend exact timing.
Duration of treatment of 5 days is consistent with the evidence and is therefore accepted.

Several different endpoints were used in the different studies. Most used 10 cm visual analogue scale ranging from a subjective assessment by participants of 0 (insignificant symptoms of jet lag) to 100 (very bad symptoms). In some studies each jet lag symptom or sleep parameters were assessed by a separate VAS and in others a global assessment of jet lag was used. In some studies the VAS was administered daily for several days after arrival and in some they were retrospectively assessed several days after arrival. In addition, scales of cognitive performance were used, such as effect on reaction time and vigilance, and scales measuring effects on mood.

Nine of the ten studies demonstrated statistically significant effects on jet lag symptoms or sleep. With respect to clinical relevance: two of the studies conducted a responders analysis (Arendt '87 and Calustrat '92) with respect to self assessed jet lag severity and both showed a considerable difference (67% and 40%, respectively) in % responders. A study (Petrie '89) showed that melatonin treated subjects took on average one day less to return back to normal sleep (2.9 days compared to 4.2 days), which may be considered as clinically relevant.

With respect to the relevance of the obtained effect, the results on global efficacy, measured on a Visual Analogue Scale score on severity of jet lag show a 44% lower rating for melatonin as compared to placebo. This global rating of subjective assessment by the treated individuals, is considered clinically relevant.

Altogether, it is considered that nine out of ten studies demonstrated statistically significant effects on jet lag symptoms (e.g. mood, cognitive) or on sleep (which is perhaps the most important jet lag symptom) and that two out of ten studies with results for responders analysis concerning global jet lag symptoms (Arendt '87 and Calustrat '92) of self assessed jet lag severity demonstrated a considerable difference (67% and 40%, respectively) in percentage responders. In addition, the study by Petrie '89 showed that melatonin treated subjects took on average one day less to return back to normal sleep (2.9 days compared to

4.2 days), which may be considered as clinically relevant and as tapping into the ability to return back to normal functioning (i.e. work).
All presented studies are included in a Cochrane Systematic Review (Herxheimer and Petrie, 2002, reviewed 2008), which concluded that melatonin (0.5 to 5 mg/day) is effective in preventing or reducing jet lag.

In conclusion, the evidence submitted, and the Cochrane review do suggest that melatonin is effective in jet lag.

IV.5 Clinical safety

The most common adverse events (AEs) reported in the published articles included headache, nausea, drowsiness and sedation. The incidence of AEs is low. There were no serious AEs or death reported.

pharmacodynamic studies and animal studies show that melatonin has strong effects on several hormones involved in the sexual maturation of pubertal female and male rats. In addition, effects of melatonin on the level of several hormones involved in reproduction have been found in mature rats and dogs. In addition, pharmacodynamic studies show effects on reducing glucose tolerance and insulin sensitivity. Likewise, the analgesic effect of melatonin may point to the possibility of interactions with opioidergic and GABAergic medications.

The MAH's conclusions on immune system adverse events and the potential of melatonin to modulate immune system function are endorsed. The cases that were identified in the literature are not a very strong signal, especially since one involved longer exposure and another additional risk factors. Nevertheless, the MAH proposes an SmPC text regarding effects on immune system (section 4.4). This is accepted. Although the evidence is not strong, it might represent additional cases that were not reported.
The fact that no cases were identified in the safety database is reassuring and support the contention that melatonin has a benign safety profile.

In addition, the evidence submitted suggest that melatonin may have an effect on fertility in women or men, on pregnancy, and on breast feeding. Although the data are sparse a warning about these effects are included in the relevant SmPC sections.

In addition, the submitted evidence also suggest that melatonin can increase plasma glucose in healthy persons and there is a potential for interaction with food. Therefore the MAH proposes to include a warning indicating that intake of melatonin with carbohydrate-rich meals may impair blood glucose control and should therefore be avoided for 2 hours before and 2 hours after intake of melatonin. This is accepted.

Although melatonin may have analgesic effects, no evidence was identified to show a potential for pharmacodynamic interactions with analgesics. Therefore no warning is deemed necessary in connection with the analgesic effect of melatonin.

An important potential risk of melatonin is its co-administration with other medications or substances that are also involved with CYP1A metabolism such as fluvoxamine, zolpidem or related drugs (zopiclone, zaleplon), which may increase the plasma concentration of either products. A warning against such co-administration is included in the SmPC of Melatonin Pharma Nord and therefore this risk is considered addressed. Likewise the risk of high exposure to melatonin in persons with renal or hepatic dysfunction is addressed in the SmPC, and therefore this risk is considered addressed as well.

Lack of evidence in children and the potential of melatonin effects on the reproductive organs in preclinical studies as well as potential long-term endocrine effects on cardiovascular, immune and metabolic systems when administered to children and adolescents warrant the proposed SmPC limitations and warnings on paediatric use, namely:

- A text in the dosing section (4.2) indicating that: "*The safety and efficacy of Melatonin Pharma Nord in children aged 0 to 18 years have not yet been established",*
- A warning in section 4.4 stating that: "*The safety and efficacy of Melatonin Pharma Nord in children and adolescents aged 0 – 18 years have not been established. Melatonin Pharma Nord should not be used in children and adolescents due to safety and efficacy concerns"*
- A text in section in 5.1 stating that: "*The safety and efficacy of melatonin in children and adolescents aged 0 – 18 years have not been established. Melatonin Pharma Nord 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".*

Altogether, the (limited) available evidence from clinical studies and post-marketing data suggests that tolerability and safety of melatonin, especially when used for a short time period, is high, with headache, nausea and drowsiness as the most frequent side effects.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Melatonine Pharma Nord.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Risk of increased effects and adverse reactions of melatonin in combination with fluvoxamine (increase of melatonin levels) - Increased sedative effects in combination with benzodiazepines and other hypnotics - Drowsiness

Important potential risks	- Off-label use in paediatric patients with sleep disorders - Risk of hyperglycaemia, particularly in diabetics and other patients with impaired glucose tolerance
Missing information	- Use in patients with renal impairment - Use in patients with hepatic impairment - Use in patients with autoimmune disorders - Use in patients with epilepsy - Use in paediatric population - Use during pregnancy or breast-feeding - Long-term safety - Fertility in women and men

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information. Limitation of the pack size to 30 tablets as a risk minimisation measure has been adopted to prevent off-label use of melatonin.

IV.7 Discussion on the clinical aspects

Altogether it is considered that efficacy of melatonin in the treatment of jet lag has been established as the majority of studies in jet lag subjects showed statistically significant and clinical relevant results. In addition the safety of melatonin is considered generally benign and it is considered that the safety issues that are identified and are adequately addressed in the SmPC.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Melatonine Pharma Nord 3 mg film-coated tablets has a proven chemical-pharmaceutical quality in view of the present European regulatory requirements. The efficacy has been demonstrated for the indication jet lag in adults and that the safety issues that were

identified are adequately addressed by SmPC warnings and the Risk Management Plan. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member state, on the basis of the data submitted, considered that well-established use has been demonstrated for Melatonine Pharma Nord and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 July 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse