COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Melatonine ACE 1 mg, 3 mg and 5 mg tablets
(melatonin)

NL License RVG: 126909 - 126911

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This module reflects the scientific discussion for the approval of Melatonine ACE 1 mg, 3 mg and 5 mg tablets. The procedure was finalised on 26 June 2023. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
BCS	Biopharmaceutics Classification System
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
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
IP	Intraperitoneal
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
UPLC	Ultra-High Performance Liquid Chromatography
VAS	Visual Analogue Scale

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the MEB has granted a marketing authorisation for Melatonine ACE 1 mg, 3 mg and 5 mg tablets, from ACE Pharmaceuticals B.V.

The product is indicated for short-term treatment of jetlag in adults.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC after an initial refusal. After the two regular assessment rounds, four quality objections remained unresolved, as well as insufficient bridging to literature. A proposal of refusal was therefore sent to the MAH. The MAH sent a written reaction and requested an oral hearing, which was held on 13 January 2022. Thereafter, additional written responses to the last remaining issues were sent by the MAH.

This national procedure concerns a bibliographical application based on well-established medicinal use of melatonin. For this type of application, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years in the specific therapeutic use. The results of non-clinical and clinical trials are replaced by detailed references to published scientific literature.

Melatonin tablets were first introduced into the European market at least ten years ago as a preoperative medication for short-term treatment of jetlag.

Aspects of well-established use are discussed in the clinical overview. The applicant refers to the registration of Bio-Melatonin in Hungary since 2003 (registration number OGYI-T_08974), for the indication jet lag. In addition to Bio-Melatonin registered in Hungary, another melatonin product has been registered in Poland since 2003 for sleep disorders related to change of time zones. Thus it is considered that in terms of time, melatonin is well-established for at least ten years in the EU community. It is acknowledged that several melatonin products for the indication jet lag are already registered in the Netherlands, based on well-established use legal base. The literature data reflects the degree of scientific interest in the use of melatonin, and is considered adequate.

Altogether it is considered that well-established use in the EU community for at least 10 years is demonstrated.

II. QUALITY ASPECTS

II.1 Introduction

Melatonine ACE are round tablets. The distinction of the three strengths is based on the embossment and the colour of the tablets, which is considered sufficient.

Melatonine ACE 1 mg is white and debossed with 'MEL 1'. It contains as active substance 1 mg of melatonin.

Melatonine ACE 3 mg is orange and debossed with 'MEL 3'. It contains as active substance 3 mg of melatonin.

Melatonine ACE 5 mg is blue and debossed with 'MEL 5'. It contains as active substance 5 mg of melatonin.

The excipients are: microcrystalline cellulose (PH102) (E460), sodium starch glycolate type A, colloidal anhydrous silica (E551), magnesium stearate (E470b), Eurolake sunset yellow (E110) (3 mg only) and Lake indigo carmine (E132) (5 mg only).

The different tablet strengths are fully dose proportional.

The tablets are packed in polyvinyl chloride/polyethylene/polyvinylidene chloride-aluminium (PVC/PE/PVdC-Al) blisters.

II.2 Drug Substance

The active substance is melatonin, an established active substance described in the British Pharmacopoeia (PB) and United States Pharmacopeia (USP). The active substance is an ivory to beige crystalline powder. The active substance demonstrates no evidence of isomerism.

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 applicant 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.

Manufacturing process

The manufacturing process consists of one synthetic and one purification step by site I and four steps by site II. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail. No class-1 solvents or metal catalysts are used in the synthesis.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets in-house requirements. Batch analytical data demonstrating compliance with this specification have been provided for two micronised and one non-micronised batches. The specification is based on the specification from the ASMF holder, with additional test for particle size distribution.

Stability of drug substance
Stability data on the active substance have been provided for six micronised batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 36 months. Based on the data submitted, a retest period could be granted of five years 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 and their functions is explained. Compatibility studies with the excipients have been performed as part of the forced degradation studies in the validation of the analytical method for related substances.

Dissolution studies are performed at three pH levels (1.2, 4.5 and 6.8) with the three strengths of test product, and compared with reference product Melatonine Tiofarma 3 mg tablets. All products show dissolution of at least 85% in all three media. Development of the dissolution test method has been sufficiently discussed. The discriminatory power of the method has not been demonstrated, however in view of the high solubility of the drug product throughout the physiological pH this is considered acceptable.

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. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation has been performed for all three strengths. Four validation batches of the 1 mg strength was performed, while three validation batches were performed for that the 3 mg and 5 mg strengths. This was because the 1 mg strength was considered non-standard batch size. An adequate commitment to complete process validation at maximal batch size has been provided, the process validation schemes are provided.

Control of excipients
All excipients and components of excipients comply with the Ph.Eur, except for the colorants, for which compliance to EC/231/2012 is stated. The provided excipients' specifications are acceptable, including additional functional related characteristics where relevant.

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, identification, average weight, diameter and thickness, assay, uniformity of dosage units by content uniformity, resistance to crushing, disintegration time, dissolution, water activity, related substances and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The ultra high performance liquid chromatography (UPLC) method for assay and related substances is considered adequately validated and suitable for the intended use. The suitability of the methods for microbiological quality testing in presence of the finished product has been confirmed.

Batch analytical data from the proposed production site has been provided of three batches per strength, of production batch size and with the final formulation (without colorants). The batch results comply with the proposed release specification. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Stability of drug product

Stability data on the product have been provided from 1 batch per strength stored at 25°C/ 60% RH (12 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Furthermore, stability data have been provided for batches with previous compositions (development batches) used in the process validation; these are considered as supportive. On basis of the data submitted, a shelf life was granted of 24 months. No specific storage conditions needed to be included in the SmPC or on the label.

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 MEB considers that Melatonine ACE 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

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 has a

hypnotic/sedative effect on cognition when given orally. The pharmacological mechanism of action in melatonin is believed to be based on its interaction with MT1-, MT2- and MT3 receptors, as these receptors (particularly MT1 and MT2) are involved in the regulation of sleep and circadian rhythms in general.

The non-clinical overview gives an adequate overview of the pharmacological, pharmacokinetic and toxicological properties of melatonin, based on *in vitro* data and data in animals. These data show that melatonin is a well-known active substance in medicinal products. No additional nonclinical studies are needed.

III.2 Pharmacology

Primary pharmacodynamics

Melatonin acts through different molecular pathways. The best characterised pathway is the activation of two types of membrane specific receptors: high affinity ML1 sites and low affinity ML2 sites (Dubocovich, 1995; Morgan et al., 1994). ML1 receptors are G protein-coupled receptors (Ebisawa et al., 1994). Activation of ML1 receptors leads to an inhibition of the adenylate cyclase in target cells. The activation of ML2 receptors, currently called MT3, leads to phospho-inositides hydrolysis. MT3 is expressed in various brain areas and has been shown to be the enzyme quinone reductase 2 (Cardinali, 1997). Melatonin also has an intracellular action by binding to cytosolic calmodulin (Benitez-King, 1993), and, to two receptors of the Z -retinoid nuclear receptors family (Becker-Andre et al., 1994). Melatonin receptors have been found in several central but also in peripheral tissues, including heart and arteries, adrenal gland, kidney, lung, liver, gallbladder, small intestine, adipocytes, ovaries, uterus, breast, prostate, and skin (Ekmekcioglu, 2006). Furthermore, they have also been detected in T and B lymphocytes. Evidence shows that there is a considerable variation in the density and location of the expression of melatonin receptors between species (Morgan et al., 1994). In a recent review it is suggested, on the basis of affinity studies showing species-dependent fluctuations *in vivo* ligand selectivity, that there are considerable species differences in melatonin receptor pharmacology (Liu et al., 2016). The effects of melatonin depend on the localisation and types of receptors binding melatonin.

In view of some data that indicate that melatonin may exert a sleep inducing effect in humans, it is suggested that melatonin induces changes that are typical for the dark period of each species. In rats with free-running circadian rhythms, oral and subcutaneous administration of melatonin resulted in a stable diurnal rhythm (Slotten et al., 1999). When melatonin was given intraperitoneally (IP) to rats either during the light period or dark period, body temperature was either elevated (during light), while it decreased during darkness (Isobe et al., 2002). The observed changes in body temperature during the light and dark periods were explained by accompanying the suppression of activity induced by melatonin. Houdek et al. (2016) demonstrated that the significant impact of long-term melatonin absence (due to a pinealectomy) on period of the central clock in the SCN and the amplitudes of the peripheral clocks in duodenum and liver suggesting that melatonin might be a redundant but effective endocrine signal for these clocks.

Jet lag disturbs hippocampal neurogenesis and spatial cognition, which represent morphological and functional adult brain plasticity. A recent study suggested that melatonin

is required to prevent cognitive impairment caused by the same environmental factors to which frequent flyers and shift workers are typically exposed to (Iggena et al., 2017). In this study mice were exposed to photoperiod alterations in order to simulate "jet lag". These mice showed reduced hippocampal neural precursor cell proliferation by 24% and impaired spatial memory performance in the water maze indicated by a prolonged swim path to the target. After IP treatment with 8 mg/kg melatonin both the cellular as well as the cognitive deficits were prevented.

To explore the nature of sleep-promoting effects of melatonin, Zhdanova et al. performed a study in macaque species (Zhdanova et al., 1998). A major advantage of these models are, in addition to the phylogenetic proximity, important similarities between humans and diurnal non-human primates. While low melatonin doses did not significantly affect nighttime sleep efficiency, higher pharmacological doses reduced sleep efficiency and increased sleep fragmentation at night, and reduced spontaneous daytime locomotor activity. Long-term melatonin treatment did not result in development of tolerance or sensitisation to melatonin effects on sleep.

Secondary pharmacodynamics

In mice, low doses of melatonin (8-16 mg/kg) had no or little behavioural effects. At doses of 64, 128 and 256 mg/kg decreased fear, reactivity, muscle tone and hypothermia were observed with dose-dependent intensity and duration. At 128 mg/kg it also showed analgesic activity in the four-plate test (Guardiola-Lemaitre et al., 1992). Raghavendra et al. showed that melatonin can reverse the increased mobility period when mice received 2.5-10 mg/kg melatonin prior to performing a swimming test. This effect was comparable with the effect of GABA-benzodiazepine (BZ) receptor agonists and was sensitive to reversal by peripheral BZ receptor antagonist, suggesting the involvement of this receptor (Raghavendra et al., 2000).

Melatonin regulates pubertal development in some juvenile mammals. In seasonal breeders, melatonin seems to act as either pro-gonadotrophic or anti-gonadotrophic according to the period of the year autumn-winter/short days or spring-summer/long days respectively. Melatonin has also been shown to influence secretion of several hormones in animals and in humans, namely the luteinizing hormone (LH) and prolactin, corticosteroids, thyroid hormones and insulin. A review from 2018 indicates that melatonin is a key player in the regulation of steroidogenesis (Yu et al., 2018). However, the melatonin-induced regulation of steroid hormones may differ among species, and the literature data indicate that melatonin has important effects on steroidogenesis and male reproduction. In female rats Lu and Meites (1973) observed that a single intravenous dose of melatonin increased serum prolactin levels. In Syrian hamsters, several authors observed either decrease or an increase of the prolactin, FSH and LH hormones (Wun et al., 1986). It is possible that the conditions of administration such as the period of the year, the time of the day or the duration of the administration period may have influenced the results. In hamsters, endogenous and cyclically administered melatonin depressed the thyroid function (Vriend et al., 1986). Melatonin in drinking water, given to blinded hamsters for 10 weeks partially restored thyroxin levels and testis weights normally associated with blinding. Melatonin caused a marked decrease of insulin secretion in response to glucose when freshly isolated rat islets were incubated with melatonin. Melatonin did not interfere with glucose metabolism as indicated by the measurement of

glucose oxidation. However, the content of the protein kinase A (PKA) catalytic alpha-subunit was significantly decreased in islets exposed to melatonin (Picinato et al., 2002).

Several papers in various species reported the effect of melatonin on the cardiovascular and respiratory systems. Chuang et al. showed that intravenous administration of 30-60 mg/kg in rats resulted in a dose-related fall in mean arterial pressure, heart rate, or serotonin release in both the corpus striatum and the hypothalamus. Bradycardia was abolished by pre-treatment with bilateral vagotomy. These results suggest that melatonin decreases brain serotonin release and results in sympathetic inhibition or parasympathetic stimulation which leads to hypotension and bradycardia in rats (Chuang et al., 1993). Additionally, Viswanathan et al. demonstrated that melatonin receptors are expressed in the cerebral arteries of the rat which form the circle of Willis. We report here that melatonin induces contraction of *in vitro* preparations of pressurised rat posterior communicating artery, in a concentration-dependent manner. This action could be inhibited by a specific melatonin receptor antagonist demonstrating that the contractile action of melatonin is mediated by its receptors in the cerebral artery (Viswanathan et al., 1997). Also studies in porcine and coronary arteries suggest the potential for melatonin to have tensive effects (Viswanathan et al., 1992; Weekley, 1993). In baboons, 0.3 to 0.4 mg/kg i.v. melatonin, caused a statistically significant increase of the cardiac output and ventricular ejection associated with a reduction in heart rate (Bosman et al., 1991). Additional studies show that at a dose of 100 mg/kg a slight decrease of heart rate and blood pressure were observed in rats (Circadin EPAR, 2007). The Q-T interval of the electrocardiogram (ECG) and the respiratory rate were not changed. Also in humans evaluation of ECG was performed and reported as not presenting any effects on the Q-T interval.

In the literature it is described that 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, confusion, and reduced activity during the first hour after getting up compared to zolpidem alone (Suhner et al., 2001). Secretion of melatonin has been shown to be affected by adrenergic agonists and antagonists, antidepressants, opiate agonists and antagonists, prostaglandin synthesis inhibitors, benzodiazepines, barbiturates and glucocorticoids. Papagiannidou et al. investigated possible interactions of melatonin with concurrently administered drugs in *in vitro* studies utilising human hepatic post-mitochondrial preparations. Similar studies were conducted with rat preparations to ascertain whether rat is a suitable surrogate for human (Papagiannidou et al., 2014). Of the drugs screened, only the potent CYP1A2 inhibitor 5-methoxypsoralen impaired the 6-melatonin hydroxylation at pharmacologically relevant concentrations, and is likely to lead to clinical interactions; diazepam, tamoxifen and acetaminophen (paracetamol) did not impair the metabolic conversion of melatonin to 6-sulphatoxymelatonin at concentrations attained following therapeutic administration. 17-Ethinhyloestradiol appeared not to suppress the 6-hydroxylation of melatonin but inhibited the sulphation of 6-hydroxymelatonin, but this is unlikely to result in an interaction following therapeutic intake of the steroid. These results indicate that species differences in the inhibition of melatonin metabolism in human and rat hepatic post-mitochondrial preparations are evident, implying that the rat may not be an appropriate surrogate of human in such studies.

III.3 Pharmacokinetics

In the study of Yeleswaram et al. (1997), the pharmacokinetics and bioavailability of melatonin was investigated in rats, dogs and monkeys after intravenous and oral administration. Melatonin is rapidly absorbed from the gastrointestinal tract. The mean oral bioavailability of 10 mg/kg of melatonin was 53.5% in rats and >100% in dogs and monkeys. The low bioavailability (16.9%) in low doses (1 mg/kg) in dogs suggests non-linear pharmacokinetics in experimental animals.

In humans, after intravenous or oral administration, melatonin is quickly metabolised, mainly in the liver and secondarily in the kidney. It undergoes hydroxylation to 6-hydroxymelatonin by the action of the cytochrome P450 enzyme CYP1A2 followed by conjugation with sulfuric acid (90%) or glucuronic acid (10%).

Melatonin seems to distribute fast through tissues with an elimination half life from serum of ~20 minutes in rats (Yeleswaram et al. 1997). A similar half-life estimate was obtained in dogs (18.6 min), while it was longer in monkeys (22.9 min). In contrast, the reported apparent elimination half-life of melatonin in humans is approximately 45 min (Harpsøe et al., 2015). Thus, it appears that the half-life of melatonin is longer in primates than in rodents. Even after brain injection it was shown that melatonin is cleared after 5 minutes in rats. The steady-state volume of distribution ranged from 1.05 to 1.48 L/kg in rats, dogs and monkeys, indicating moderate tissue distribution of melatonin in these animals. In humans mean distribution values have been reported of 0.55 L/kg (Mallo et al., 1990) and 1.6 (0.9) L/kg and 2.0 (0.8) L/kg (Andersen et al., 2016). These results indicate that humans show a significantly reduced distribution when compared to animals, since in humans melatonin was given at lower doses. Melatonin easily crosses the placenta as the blood-brain barriers and blocks oxidative, excitotoxic and inflammatory pathways, all involved in the pathogenesis of perinatal brain damage caused by preterm birth (summarised by Biran et al., 2014) . Literature data show that most circulating melatonin is bound to albumin, to the same extent in rat as in humans (Cardinali et al., 1972). *In vitro* experiments using radiolabelled melatonin, showed that melatonin also binds to haemoglobin and calmodulin (Benítez-King et al., 1993).

Approximately 5% of serum melatonin is excreted unmetabolised in urine. The principal metabolite, the 6-sulfatoxymelatonin (a sulphate conjugate of 6-hydroxymelatonin 6-SM), is inactive, and its urinary excretion reflects melatonin plasma concentrations (Lynch et al., 1975). Plasma levels can be also measured directly or indirectly assessed through salivary measures. A reverse relation between bioavailability of melatonin and the 6-SM concentrations area under the curve has been shown, the low bioavailability being explained by an important hepatic first pass (Di et al., 1997). *In vitro* metabolism studies using liver microsomes also indicate that 6-hydroxylation is the major route. Also 5-methoxyindoleacetic acid appears to be formed by deacetylation of melatonin followed by deamination.

As melatonin is mainly metabolised by CYP1A2 there is potential for pharmacokinetics interactions with other drugs that either induce or inhibit CYP1A2 metabolism. Drugs known to increase endogenous or exogenous melatonin, likely through ([non]-competitive) inhibition of melatonin metabolism, are fluvoxamine, cimetidine, psoralens, oestrogens, and caffeine. Overall, interactions that increase melatonin plasma concentrations are expected to be of

minimal clinical concern. Administration of melatonin doses as high as 1 g did not result in serious or severe side effects. Drugs that are known to decrease either endogenous or exogenous melatonin, through CYP1A2 induced metabolism are carbamazepine and smoking. The production of endogenous melatonin is mainly regulated by noradrenaline release in the perivascular space of the gland during the dark period. Drugs that act on the release of noradrenaline, and that were administered together with melatonin in a drug-drug interaction study are desipramine and oxaprotiline. For the following drugs, listed in SmPCs of melatonin products currently registered in The Netherlands, no clinical studies have been identified for quinolones and rifampicin.

III.4 Toxicology

Single-dose toxicology

Melatonin has a very low acute toxicity when administrating single oral doses. In humans, melatonin may cause minor adverse effects, such as daytime sleepiness, dizziness, headache and loss of appetite. In animals, an LD50 (lethal dose for 50% of the subjects) after oral dose of 1250 mg/kg and 3200 mg/kg have been reported for the mouse and rat, respectively, which is tens of thousands times more than the maximum recommended human dose (MRHD) (Sugden, 1983).

Repeat-dose toxicology

Most of the data available is obtained from studies performed for the registration of a product in 2007. Repeat dose studies have been performed in rats, mice and dogs. In general, the toxicological profile of repeated administration is low.

In rats, the toxicological profile of melatonin after a 90-day period of administration was low but very low doses were used in the study (0.3, 1.2 and 6 mg/kg/day). The toxicokinetic data from the study showed mean plasma concentrations up to 50 pg/ml, which are lower than those expected to be reached in humans. A decreased body weight gain of the animals at 1.2 mg/kg/day (males) and 6.0 mg/kg/day) (males and females). Also decreased testis and increased kidney relative weights were observed at 6 mg/kg/day (Circadin EPAR, 2007). An additional 26-weeks study as well as the 13 weeks study showed increased haemoglobin concentration and platelet counts were observed at 75 and 150 mg/kg/day treated animals. Increased liver weights with minor centrilobular hepatocytic hypertrophy were observed. Increased testes, prostate and epididymides weights were seen in males administered 75 and 150 mg/kg/day. At 26 weeks, macroscopically dark thyroid was also recorded in several animals dosed 150 mg/kg/day. Microscopically, minor liver hypertrophy was seen in some high dose animals but reported as less obvious than in the 13 weeks treated group. Toxicokinetics showed that melatonin was systemically absorbed at all dose levels of melatonin at the 13, 26 and 104 week time-points in both sexes. In general, when comparing data from day one and seven, the Cmax values of the females were higher than those of the males and the maximum concentration was achieved over a longer period of time. There appeared to be a sex difference in increase of AUC values compared to the increase in dose received. All values were reduced upon repeated exposure of melatonin suggesting reduced absorption, increased elimination or induction of enzymes. From data obtained for the complete period (104 weeks), there was no apparent sex difference observed and there was no accumulation of melatonin over the full dosing period. In the repeat-dose toxicity studies

in rats the plasma concentrations measured along the study decreased along the exposure time. No further AUC values were determined. The systemic exposures in rats along the study are therefore not evaluable and appropriate animal to human exposure ratios cannot be calculated.

Melatonin might cause damage to the retina. Rats were treated with oral doses of melatonin in the light period or early in the dark period (and some rats exposed to high intensity illumination (HII)) after which the effect of the photoreceptors were investigated (Weichmann et al., 2008). The results of this study confirmed that melatonin increases the susceptibility of photoreceptors to light-induced cell death in non-pigmented rats. It further suggests that during the dark period, melatonin administration alone (i.e., HII exposure) to pigmented male rats may have a toxic effect on retinal cells. These results suggest that dietary melatonin, in combination with a brief exposure to HII, induces cellular disruption in a small number of photoreceptors. Chronic exposure to natural or artificial light and simultaneous intake of melatonin may potentially contribute to a significant loss of photoreceptor cells in the aging retina.

In hypercholesterolemic mice feeding with an atherogenic diet supplemented with melatonin highly increases the surface of atherosclerotic lesions in the proximal aorta (Tailleux et al., 2002). These observations occurred without detectable lipidic or glucidic phenotype alteration. Melatonin treatment increased highly the sensitivity of atherogenic lipoprotein to Cu(2+) and gamma-radiolysis generated oxyradical *ex vivo* oxidation during the fasting period. Moreover, these altered lipoproteins were less recognised by the LDL receptor metabolic pathway of murine fibroblasts while they transferred many more cholesteryl esters to murine macrophages, suggesting that caution should be taken as regards high melatonin dosage in hypercholesterolemic patients.

In the 6-month repeat dose toxicity study in dogs where 0.4, 1.5 and 8 mg/kg melatonin were used, increased serum glucose levels were observed at some time points of the study. Microscopic examination revealed pituitary gland and parathyroid cysts, adenomyosis of the uterus, capsular fibrosiderosis of the spleen and cytoplasmatic rarefaction of hepatocytes consistent with the presence of glycogen. Based on toxicokinetic data the Cmax values obtained with the mid and high doses were high in excess to the levels to be reached in man under therapeutics (Circadin EPAR, 2007).

Genotoxicity

The mutagenic potential of melatonin and its metabolite 6- hydroxymelatonin has been investigated using a reduced Ames test and three strains of Salmonella typhimurium (TA 97, TA 98, and TA 100) (Neville et al., 1989). Neither compound exhibited mutagenicity whether in the presence or absence of an activation system derived from rats induced with Aroclor 1254. Further literature data report that melatonin and two related compounds, 6-hydroxymelatonin, the principal metabolite of melatonin, and 5-methoxyindoleacetric acid (5-MIAA) were screened for relevant information associating these chemicals with respect to mutagenic or carcinogenic effects (DEREK system). No structural alerts were identified. Overall, it is concluded that melatonin does not present genotoxic potential (Circadin EPAR, 2007). No further literature have been found that describe the mutagenic potential of

melatonin. However, multiple papers describe the potential protection of melatonin to compound induced genotoxicity due to its antioxidant property.

The carcinogenic potential of melatonin was evaluated in one long-term rat study and a short term mouse study (US, NTP study) (Circadian EPAR, 2007). In the combined rat chronic toxicity and oncogenicity study rats were treated orally by gavage with 15, 75 and 150 mg/kg/day for 104 weeks. With regard to tumourigenic potential, an increase in thyroid follicular cell neoplasia was observed in males at 150 mg/kg/ day, but was not statistically significant. Additional investigation of potential mechanism of action was conducted in a follow-up study using blood samples from this study. An increase in the incidence of pituitary adenomas did reach statistical significance (p=0.036) in males at 150 mg/kg/ day. Thyroid follicular cell hypertrophy and a slight increase in thyroid follicular cell neoplasia were observed in males in the combined toxicity and oncogenicity study. Although the increase in thyroid follicular cell neoplasia following exposure to high doses of melatonin (150 mg/kg/day) was not statistically significant, available blood samples from rats in that study were examined for plasma levels of TSH, T3 and T4, in order to try to clarify the mechanism for increased thyroid tumours. The data from this study on TSH, T3 and T4 does not suggest any effect of melatonin on the levels of these hormones. The short-term carcinogenicity study in transgenic mice did not show any tumorigenic potential (Rao et al., 2000). In this study four-week-old hemizygous TG.NK female mice with MMTV/c-neu oncogene fed NTP-2000 diet were gavaged with 0.05-0.2 ml of flaxseed oil as the source of omega-3 rich PUFA, or melatonin at 50-200 mg/kg or a combination of 0.10 ml flaxseed oil and 50 mg/kg melatonin for 30 weeks. Melatonin did not show any tumorigenic potential in this model. In contrary melatonin has the potential to markedly delay the appearance of palpable mammary tumours. These data take together indicate that melatonin does not show tumorigenic potential. No additional data on the carcinogenic potential of melatonin were found in literature.

Reproductive and developmental toxicity

In mammals, including humans it has been shown that melatonin controls the reproductive cycle. Melatonin influences the levels of LH and FSH across many species and inhibits ovulation. (Voordouw et al., 1992).

Several studies in mice and rats showed that melatonin had no toxic effect on embryo-foetal development. The effect of melatonin on embryonic development was investigated in a study in which time-mated Sprague-Dawley-derived (CD) rats were treated with increasing doses of melatonin (1 to 200 mg/kg) (Jahnke et al., 1999). Melatonin had no effect on prenatal survival, foetal body weight, or incidences of foetal malformations/variations. The study showed a maternal toxicity NOAEL and LOAEL of 100 and 200 mg/kg/day, respectively, and the developmental toxicity NOAEL was > or = 200 mg/kg/day. Prenatal and postnatal development, including maternal function A recent study in rats investigated the effect maternal melatonin deprivation (MDD) during gestation and lactation to the off-spring (Motta-Teixeira et al., 2018). Conversely, female offspring neurodevelopment was not affected. In male MMD significantly delayed the appearance of physical features, neurodevelopment and cognition, which could be reversed by maternal melatonin replacement therapy. Therefore, the use of melatonin during lactation should be avoided. Animal studies further suggest that melatonin can downregulate the pituitary/gonadal axis resulting in hypogonadism and/or delayed puberty (Ebling et al., 1989).

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Melatonine ACE is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

This product has been granted a market authorisation for well-established use. 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 MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Melatonin is a well-known active substance with established efficacy and tolerability. 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 MEB agreed that no further clinical studies are required.

The MAH did not perform clinical pharmacology studies. The current application is based upon a well-established use application (Article 10a), i.e. it claims that melatonin has a well-established medicinal use, with recognised efficacy and an acceptable level of safety on the basis of bridging to detailed scientific literature.

IV.2 Pharmacokinetics

Melatonin is a well-known active substance with established efficacy and tolerability. 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 MEB agreed that no further clinical studies are required.

IV.3 Pharmacodynamics

The precise mechanism of action of melatonin is not known, although it seems that MT1 receptors in the suprachiasmatic nucleus (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 available PD data 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 ten 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. Case reports concerning autoimmune reaction in response to treatment with melatonin have been published. Please refer to the safety section.

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 oestradiol levels in healthy women.

In conclusion, the pharmacodynamics of melatonin are well known and established. The rather concise discussion on melatonin pharmacodynamics the MAH has presented is complemented with data presented in the safety section.

IV.4 Clinical efficacy

Altogether twelve controlled studies are presented in support of the jet lag indication, from which ten are considered relevant for the efficacy claim. 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 et al., 1987, Arendt & Aldhous., 1988, Petrie et al., 1989, Claustrat et al., 1992, Petrie et al., 1993, Nickelsen 1991, Edwards et al., 2000,) three studies included around 60 subjects per arm (Suhner et al., 1998a, Suhner et al., 1998b and Spitzer et al., 1999).

The dose range used in the studies was 0.5 mg to 8 mg. However, results of studies with low dose of immediate release suggest that such low doses are not effective and a higher than 5 mg dose is not clearly more effective. The Cochrane review concludes that doses between 0.5 mg and 5 mg appear to be similarly effective, and that as 5 mg may be a higher dose than necessary, a dose of 1 or 3 mg may be preferable to start with. Therefore recommending a dose of 1-5 mg as in the proposed posology, is supported by the evidence. Individual variations in melatonin metabolism exist, there is no strong basis to recommend exact timing.

Duration of treatment of 6 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 (VAS) ranging from a subjective assessment by participants of zero (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.

Eight 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 et al., 1987 and Claustrat et al., 1992) with respect to self assessed jet lag severity and both showed a considerable difference (67% and 40%, respectively) in % responders. The study by Petrie et al., 1989 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 VAS 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 eight of the 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 of the ten studies with results for responders analysis concerning global jet lag symptoms (Arendt et al., 1987 and Claustrat et al., 1992) of self-assessed jet lag severity demonstrated a considerable difference (67% and 40%, respectively) in percentage responders. In addition, the study by Petrie (1989) 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 & 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 event (AE) 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.

There are literature references suggesting that melatonin can increase seizure frequency, although clear causality between melatonin and epilepsy/seizure activity cannot be considered established. Nevertheless as some reports of increase in seizure frequency exist, a warning in SmPC section 4.4 is considered warranted and is included in the SmPC.

Secondary pharmacology of melatonin suggest effects on the immune system. These effects may call for caution in using melatonin in immune compromised patients. Case reports concerning autoimmune reaction in response to treatment with melatonin have been published. The applicant proposed a warning text for Section 4.4 of the SPC indicating that melatonin is not recommended in patients with autoimmune diseases, which is accepted.

There is evidence suggesting that melatonin can increase plasma glucose in healthy persons and there is a potential for interaction with food. Therefore the applicant 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 2h before and 2h after intake of melatonin. This is endorsed and adequately addressed in SmPC sections 4.2 and 4.4.

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

The SmPC advices not to use melatonin in children, due to lack of evidence in children. This is accepted, and the SmPC is considered to adequately address paediatric population.

Altogether, the available evidence from clinical studies 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 ACE.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	Use in children Delay of development sexual maturation
Missing information	Use during pregnancy

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

This procedure concerns a well-established use application for melatonin. For this authorisation, reference is made to literature. No new clinical studies were conducted. The pharmacokinetics of melatonin can be considered well established. The bridge to the products used in the literature to claim well-established use is established as adequate justification has

been provided by the MAH. Risk management is adequately addressed. The clinical aspects of this product are approvable.

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.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Melatonine Tiofarma, RVG 120771-120773. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Melatonine ACE 1 mg, 3 mg and 5 mg have a proven chemical-pharmaceutical quality. Melatonine ACE is a well-known medicinal product with an established favourable efficacy and safety profile.

On 30 july 2021, the MEB submitted an intention of refusal to the applicant. An oral hearing was requested and granted on 13 January 2022. The following objections were discussed and additional information was given relating to the quality of the colorants, chosen dissolution medium, maximum batch size and stability data in both blister and container packaging. In the Board meeting of 3 March 2022, the initial application of Melatonine ACE was rejected due to insufficient (indirect) bridging to the literature and four outstanding objections. The MAH argued that indirect bridging was sufficient as the 10a Guidelines did not specify whether bridging should be direct or not. The responses provided by the MAH demonstrated that the positives outweighed the negatives, therefore granting a positive recommendation.

The national procedure was finalised with a positive outcome on 26 June 2023.

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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
Type IAin: B.II.b.1.b **Type IAin: B.II.b.1.a** **Type IAin: B.III.1.a.1** **Type IA: B.II.b.2.a**	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Primary packaging site Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product • Secondary packaging site Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: for an active substance, for a starting material/reagree/intermediate used in the manufacturing process of the active substance, for excipient • European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. o New certificate from an already approved manufacture Change to importer, batch release arrangements and quality control testing of the finished product • Replacement or addition of a site where batch control/testing takes place	No	09-08-2024	Approved	-

Type IB: B.II.b.3.z (2x)	Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product • Other variation	No	09-09-2024	Approved	N/A
Type IA; B.II.b.3.a (3x)	Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product • Minor change in the manufacturing process.	No	05-11-2024	Approved	N/A
Type IB: B.II.f.1.d **B.II.f.1.b.1**	Change in the shelf-life or storage conditions of the finished product • Change in storage conditions of the finished product or the diluted/reconstituted product Change in the shelf-life or storage conditions of the finished product • Extension of the shelf life of the finished product ○ As packaged for sale (supported by real time data)	Yes	23-12-2024	Approved	N/A