COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Melatonine Tiofarma 1 mg, 3 mg and 5 mg tablets

(melatonin)

NL License RVG: 120771-120773

Date: 24 October 2019

This module reflects the scientific discussion for the approval of Melatonine Tiofarma 1 mg, 3 mg and 5 mg tablets. The marketing authorisation was granted on 8 October 2019. 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
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
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Melatonine Tiofarma 1 mg, 3 mg and 5 mg tablets, from TioFarma B.V.

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

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

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 national 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 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).

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

II. QUALITY ASPECTS

II.1 Introduction

1 mg tablet – white to off-white, hexagonal tablets with the inscription “MELA 1” on one side and a score line in the middle of the other side. Each tablet contains 1 mg melatonin.
3 mg tablet – white to off-white, oblong tablets with the inscription “MELA 3” on one side and a score line in the middle of the other side. Each tablet contains 3 mg melatonin.
5 mg tablet – white to off-white, round tablets with the inscription “MELA 5” on one side and a score line in the middle of the other side. Each tablet contains 5 mg melatonin.

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

The tablets are packed in white opaque PVC/PVdC-aluminium blisters and white opaque polypropylene containers with a white opaque polypropylene lid.

The excipients are: silicified microcrystalline cellulose, lactose monohydrate, sodium starch glycolate type A, talc (E553b) and magnesium stearate.

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 Pharmacopoeia (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 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.

<u>Manufacturing process</u>
The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

<u>Quality control of drug substance</u>
The active substance specification is considered adequate to control the quality and includes tests for appearance, colour, identification (IR, HPLC), solubility, appearance of

solution, melting point, water content, assay, purity, related substances, heavy metals, sulphated ash, residual solvents and particle size. The active substance specification is set as per BP monograph with the addition of tests for residual solvents. Limits in the specification have been justified and are considered appropriate for adequate quality control. Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance

Stability data on the active substance have been provided for ten full batches stored at 25°C/60% RH (12 to 60 months) and 40°C/75% RH (6 months). No significant changes or trends have been observed. The claimed re-test period of 60 months without special storage conditions is sufficiently justified.

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 explained.

Dissolution studies are performed with the test product, showing fast dissolution, over 85% is dissolved in 15 minutes. A comparison is made with a two suitable reference products. The MAH made plausible that the compositions and release characteristics of the products used in the literature studies are comparable to those of the proposed products as is required for a well-established use application.

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. In process controls are performed during the compression step. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for a sufficient amount of batches in accordance with the relevant European guidelines.

Control of excipients

All excipients and components of excipients comply with the Ph. Eur. These specifications are acceptable. Furthermore, additional justification on the related characteristics has been provided.

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, average mass, uniformity of mass, disintegration time, hardness, friability, identification, assay, related substances, uniformity of dosage units, microbiological purity and dissolution. 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 for three full-scale 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 three batches of each strength stored at 25°C/60% RH (up to 36 months), 30°C/65%RH (up to 36 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 24 months for the 1 mg strengths and for 36 months for the 3 mg and 5 mg strengths. The labelled storage conditions are "Store below 25°C. Store in the original package in order to protect from light".

In-use stability data has been provided demonstrating that the product remains stable for 30 days following first opening of the container with 30 tablets

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 Tiofarm 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 Pharmacology

Melatonin is involved in many physiologic processes, including circadian rhythms, mood regulation, anxiety, sleep, appetite, immune responses and cardiac functions. Several studies have shown that melatonin plays an important role in the entrainment of circadian rhythms. Melatonin exerts its biological effect by binding to the membrane bound MT1 and MT2 receptors. Literature was provided regarding the role of melatonin in circadian rhythms and the receptors involved. The amount of data on safety pharmacology was limited. However, additional non-clinical data are not necessary considering the generally mild safety profile of melatonin.

III.2 Pharmacokinetics

Following oral administration, large differences in bioavailability were observed between species and, in dogs, also between doses. Melatonin is metabolised mainly by CYP1A2 with minor contributions from CYP2C19, CYP1A1 and CYP1B1 and excreted mainly via the urine. Interactions are possible with drugs that modulate the expression of CYP1A2. The metabolism of melatonin may be inhibited by fluvoxamine, 5-methoxypsoralen and 17α-ethinyloestradiol. Adequate warnings are included in section 4.5 of the SmPC. No data were provided regarding the pharmacokinetic distribution (only regarding the distribution of the melatonin receptors) and regarding the possibility of pharmacokinetic interactions on the transporter level. However, considering the clinical experience with melatonin, it is not expected that additional non-clinical information will change the overall conclusions.

III.3 Toxicology

Melatonin did not induce relevant toxicity in mice and rats. Although melatonin was found to induce DNA adducts in vitro, overall information does not indicate that melatonin is genotoxic. No 2-year carcinogenicity study has been performed with melatonin. A carcinogenicity study with melatonin is not necessary because it is a substance naturally produced by the body and it is not intended for chronic administration. Melatonin had no effect on the embryo-foetal development in rats. In cats, subcutaneous melatonin implants were found to decrease sperm count and sperm motility and quality. Estimated maximal daily dose was not much higher than the maximum human dose. An effect on sperm production and quality can therefore not be excluded. This has been added to section 5.3 of the SmPC.

III.4 Ecotoxicity/environmental risk assessment (ERA)

An ERA was not performed apart from a statement that Melatonin Tiofarma is intended to be a substitute for melatonin tablets already on the market. In addition, considering the human metabolism of melatonin it is not expected that higher doses of the free melatonin or metabolites will be found in for example waste water. This is further supported by the fact that melatonin is a hormone secreted by humans and is already present in the environment. The MAH has provided sufficient justification that the registration of this melatonin product will not lead to an increase in environmental exposure. ERA studies are therefore not required.

III.5 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of melatonin are well known are well known. As the active substance is widely used and well-known, no further studies are required.

IV. CLINICAL ASPECTS

IV.1 Well-established use

Melatonin is widely available in the EU as nutritional supplement and for the professional market. Melatonin 1 to 5 mg tablets have been available for the professional market in countries in the European Union (including the Netherlands) for the past 14 years. A 3 mg immediate release tablet is nationally approved and available in Hungary. Another immediate release tablet is nationally approved and available in Poland.
The provided marketing authorisation dates of two registered melatonin products are older than the required ten years. The ten-year criterion can be considered fulfilled for the indication jet-lag. High degree of scientific interest in melatonin for at least 10 years has been demonstrated in jet lag. This is supported by studies retrieved from the literature. The reports from Dutch sleep clinics suggest that melatonin is used to a smaller extent in jet lag than in circadian rhythm sleep-wake disorders, however the Dutch College of General Practitioners acknowledges melatonin as treatment for jet lag.

IV.2 Bridging of clinical data

In the available literature presents a large variety of products. However, in most literature articles, a description of the product composition (e.g. melatonin mixed with lactose) or the manufacturer is presented.
As melatonin can be considered a BCS Class I drug, this bridging can be done by showing comparable *in vitro* release of the Melatonin Tiofarma tablets to that of the melatonin formulations used in literature relevant for the acceptable indication. The products at issue concern those described in literature i.e. Penn Pharmaceuticals and a simple magistral formulation of which the Penn Pharmaceutical is considered to be the most important from pharmacokinetics and clinical point of view. The results of both products show that in water, pH 1.0 and pH 4.5 over 85% is dissolved within 15 minutes. In pH 6.8, the magistral formulation shows somewhat lower dissolution at 15 minutes. The results of the magistral formulation is therefore considered as an outlier. Criteria as laid down for an Article 10a (well established use) MAA are considered to be fulfilled, sufficient data is provided to be able to bridge between the product applied for and the products described in literature.

Biowaiver of strength
For the biowaiver of strength, dissolution results for the 1, 3 and 5 mg product of Tiofarma are provided. These result show that for all product strengths and in all media, over 85% is dissolved in 15 minutes. These results are suitable to accept the biowaiver of strength.

IV.3 Pharmacokinetics

Absorption
The bioavailability reported in the literature for orally administered melatonin in an immediate release formulation at the dose of interest (between 1 and 5 mg) is low with a large inter-individual variation. Bioavailability ranged from 1 to 31%. The low and variable

bioavailability is attributed to a considerable first pass effect and to large inter-individual differences in extent of absorption from the gastro-intestinal tract
For oral immediate-release formulations, in various studies when doses of 0.5 mg to 6 mg melatonin were administered, t_{max} occurring after 30 to 60 minutes were mostly observed. In the studies that investigated doses relevant to the current application (1 mg – 6 mg melatonin), the dose-normalised C_{max} ranged from 450 to 3700 pg/ml/mg dose. From the three studies that directly compared 2 or more doses, a pattern of a dose-dependent increase in C_{max} could be observed.

Distribution
Melatonin has a volume of distribution at steady state of ~35 L. About 60 to 70 % of plasma melatonin is bound to albumin and none is bound in the cerebrospinal fluid.

Metabolism
Most of the melatonin in the general circulation is converted by CYP1A to 6-hydroxymelatonin in the liver, which clears 92-97% of circulating melatonin on a single pass. The 6-hydroxymelatonin is conjugated to the sulphate derivative 6-sulfatoxymelatonin which accounts for 50-80% and the glucuronide accounting for 5-30% of the (urinary) excreted melatonin. The remaining melatonin is excreted as 5-methoxyindoleacetic acid, unchanged, and the non-indolic metabolite N1-acetyl-5-methoxykynurenamine.

Excretion
The melatonin clearance from blood shows a biphasic pattern of first-order kinetics, corresponding to a bi-exponential decay. The half-life of melatonin ranges from 35-70 minutes. The clearance for intravenously administered melatonin ranged from 37.8 to 94.3 L/h. Excretion is primarily as metabolite via urine.

Special populations
C_{max} and AUC are higher in females compared to males, but no significant gender difference in half-life and total body clearance and volume of distribution normalised to body weight. The elimination half-life is similar in males and females. There appear to be no age differences for the pharmacokinetic parameters.
Decreased liver function may have an impact on melatonin metabolism and therefore caution should be taken when giving melatonin to patients with impaired liver function.

Interactions
Melatonin is extensively metabolised by CYP1A2 and to a minor extent by CYP2C19. Other drugs that are substrates, inhibitors or inducers of these isozymes could affect the pharmacokinetics of melatonin. Conversely, melatonin could also affect the pharmacokinetics of other drugs, metabolised by the same hepatic enzymes.
Fluvoxamine increased the AUC of melatonin due to inhibition of the melatonin metabolism. Furthermore, in another clinical study a significant inhibitory effect of oral contraceptives on the CYP1A2-catalysed melatonin metabolism was observed. Also caffeine (CYP1A2 inhibitor) and smoking (inducer of CYP1A2) affect melatonin metabolism. Concomitant administration of melatonin with 8-methoxypsoralen (8-MOP) led to increased melatonin levels most likely due to metabolism inhibition. Furthermore, a potential drug-drug interaction between melatonin and warfarin is reported in literature.

Warfarin is a racemate and consists of R-warfarin and *S*-warfarin. *R*-warfarin is metabolised by CYP1A2, 2C8, 2C9, 2C19, and 3A4. In contrast, *S*-warfarin is only metabolised by CYP2C9. A potential drug-drug interaction of melatonin with warfarin could occur due to inhibition of the metabolism of the *R*-isomer.

IV.4 Pharmacodynamics

The precise mechanism of action of melatonin is not known, although it seems that MT1 receptors in the suprachiasmatic nucleus and MT2 receptors in the retina and the hypothalamus are involved. However, other mechanisms of action, including those that do not involve the MT1 and MT2 receptors, cannot be excluded (e.g. serotonin receptors in the SCN).
The presented studies show mixed results with respect to sleep parameters after exogenous melatonin administration. While studies by Pires and Dollins showed decrease in sleep latency, this was not observed in the studies by Wyatt and Satomura. Unfortunately these studies did not investigate effects on wake-up time.
The results of the study by Dollins in general suggest that there is a dose response relationship between 0 and 1 mg and no added effect of the 10 mg over the 1mg (although there may be an added effect on the cognitive endpoints). Since the study demonstrated a relationship between dose and plasma concentration, the dose response relationship is also indicative of a relationship between plasma concentration and response.
Dose response was also observed in the study by Satomura regarding sleep parameters, as well as rectal temperature with 1 and 3 mg dose. However, in the studies by Wyatt and Pires, no dose response was observed.
All studies mentioned above used a fast-release formulation of melatonin. This is important because it was found that fast-release melatonin treatment improved sleep initiation, whereas sustained-release melatonin was more effective for sleep maintenance (sleep efficiency) (Haimov 1995, Jan 2000). Jan and colleagues (2000) even showed with their studies that fast-release of melatonin was most effective when there was only a delayed sleep onset (Jan 2000).
The applicant has submitted a limited discussion on secondary pharmacology. Available human data suggests melatonin effects on immune system, fertility, glycaemic control.

IV.5 Clinical efficacy

The MAH has described their search strategy of the studies regarded pivotal for the evaluation of efficacy in subjects in detail including a step-wise approach for inclusion/exclusion of studies. The chosen exclusion criteria e.g. different doses than the proposed posology, prolonged-release formulations, add-on treatment, are endorsed. The MAH has also defined sleep parameters/endpoints that had to be included in the publication in order to be included in the data package. For the jet lag indication, different parameters related to re-adjusting to regular sleep-wake cycle were required.

Study design
All studies were randomized double-blind placebo-controlled studies in which either melatonin or placebo was administered. Two studies included a comparative caffeine (Beaumont 2004) and zolpidem/zolpidem+melatonin combination (Suhner 2001).

Study population
All trial participants were healthy volunteers who were in the country of origin for at least 2 weeks traveling over 6 up to 10 time zones eastward. These volunteers needed to adapt to the day/night rhythm at the destination relatively quickly for work purposes. Two trials included healthy volunteers with a history of experiencing discomfort or jet lag after an eastward journey (Claustrat 1992, Arendt 1987).
In the seven trials a total of 461 participants were included (265 treated with melatonin and 151 with placebo), with an average age between 18 and 68 years old which was evenly distributed across the trials.

In most studies 5 mg melatonin was administered on a daily basis. Exceptions are the studies by Comperatore (1996) and Claustrat (1992) in which daily dose of 10 mg and 8 mg melatonin were administered. Suhner (1998) studied two different doses of immediate-release melatonin (0.5 mg, 5 mg) and 2 mg prolonged-release melatonin in comparison to placebo.
In all but one study (Suhner 1998), melatonin treatment was already started on the day of flying. In the study by Comperatore (1996) it was even started two days before. Timing of administration of melatonin or placebo on the day of departure ranged from 16.00 to 23.00h local time. Some studies (Claustrat 1992, Edwards 2000) adjusted the time of administration at departure to the time at the destination. Melatonin was taken for 3-5 days post-flight with administration time ranging from 17.00 -24.00h.

Results
In 6 out of seven trials some participants dropped out (5.9 to 33.3%). The main reasons for discontinuation in the trials were noncompliance with medication intake or study procedures, work schedules and instrumentation difficulties (Suhner 1998, 2001, Arendt 1987, Comperatore 1996, Edwards 2000). Some withdrew on medical grounds due to pregnancy or to minor travel-associated illness (Suhner 1998, Edwards 2000). One trial did not specify the reasons for drop out but did stretch that it was not due to side effects (Claustrat 1992). In one trial 9% dropped out because of adverse events, however, this trial included an extra treatment group with zolpidem and it is not clear to which treatment the participants dropping out were randomized. The events were not specified but were reported as not serious (Suhner 2001).

Table 1. Sleep parameters for individual pivotal studies in jet lag

Study	***Sleep onset latency***
Beaumont 2004	Significantly less than placebo
Suhner 1998	Decreased compared to placebo
Claustrat 1991	Decreased, but not reaching significance compared to placebo
Arendt 1987	Decreased compared to placebo
Edwards 2000	Ease in getting to sleep not different from placebo

Comperatore 1996	-
Suhner 2001	Not significantly different from placebo
Study	***Total sleep time***
Beaumont 2004	No sign from placebo
Suhner 1998	Increased compared to placebo
Claustrat 1991	-
Arendt 1987	-
Edwards 2000	Ability to stay asleep not different from placebo
Comperatore 1996	Significantly longer sleep duration than placebo
Suhner 2001	Not significant from placebo
Study	***Number of awakenings***
Beaumont 2004	Time awake not significantly different from placebo
Suhner 1998	Less time awake compared to placebo
Claustrat 1991	-
Arendt 1987	No difference
Edwards 2000	-
Comperatore 1996	-
Suhner 2001	Not significant from placebo
Study	***Sleep quality***
Beaumont 2004	Improved at first and second night
Suhner 1998	Improved compared to placebo
Claustrat 1991	-
Arendt 1987	Improved as compared to placebo
Edwards 2000	-
Comperatore 1996	-
Suhner 2001	Not significant from placebo

Four out of seven studies demonstrated statistically significant effects on jet lag symptoms or on sleep. Two studies with results for responders analysis (Arendt 1987 and Claustrat 1991) of self-assessed jet lag severity demonstrated a considerable difference (67% and 40%, respectively) in percentage responders.
The Cochrane Systematic Review (Herxheimer 2008) of randomised placebo-controlled trials with melatonin interventions for alleviating jet lag, which included most of the submitted studies reviewed in this report and with subjective ratings of jet lag as the main outcome, concluded that melatonin (0.5 to 5 mg/day) is effective in preventing or reducing jet lag.

Altogether it is considered that efficacy in jet lag has been demonstrated, including patient reported functioning. The Cochrane Review states that daily doses of melatonin between 0.5 mg and 5 mg are similarly effective, except that people fall asleep faster and sleep better after 5 mg than 0.5 mg. Therefore the proposed dosing of 1 mg to 5 mg is accepted.

IV.6 Clinical safety

Studies and reviews are in agreement that the side effects profile of melatonin is rather benign when used in short-term. The most common adverse events reported in the

published articles included headache, nausea, drowsiness and sedation. The incidence of adverse events is low. There were no serious adverse events or death reported. Because of concerns for long term safety effects on development use during pregnancy and breast feeding and use in children is discouraged.
The risk of off-label use is considered important and has been addressed in the SmPC and also by limiting the pack size to 30 tablets. 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 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.
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 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.

IV.7 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 Tiofarm.

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

Important identified risks	None
Important potential risks	- Increased sedative effects in combination with benzodiazepines and other hypnotics - Risk of increased effects and adverse reactions of melatonin in combination with fluvoxamine (increase of melatonin levels)
Missing information	- Use in children - Use in patients with renal and liver impairment - Use in patients with epilepsy - Use in patients with auto-immune disorders - Long term effects - Use in pregnancy and lactation

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

IV.8 Discussion on the clinical aspects

Criteria as laid down for an Article 10a (well established use) application are considered to be fulfilled, sufficient data is provided to be able to bridge between the product applied for and the products described in literature.

Beneficial effects
Treatment with melatonin is efficient in alleviating symptoms of jet lag, in particularly after eastward flights over several time zones. In the presented data, statistically significant effects on jet lag symptoms or on sleep were demonstrated. Efficacy has also been shown with regard to subjective ratings of jet lag in a Cochrane Systematic Review: the mean difference to placebo in global jet-lag ratings (a meta-analysis of four studies) was -19.52 (95% CI -28.13 - -10.92) ($p<0.001$)

Unfavourable effects
Based on the provided data the nature of the AEs reported in the published articles seems mild, with headache, nausea and dizziness being the most common, and the incidence of AEs is low. Concerns about safe use have all been addressed appropriately in the SmPC.

The risk of off-label use is considered important and has been addressed in the SmPC and also by limiting the pack size to 30 tablets.

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 Tiofarma 1 mg, 3 mg and 5 mg tablets have 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.

In the Board meetings of 1 June 2017, 27 September 2018 and 22 November 2018, the following was discussed:

- The abridgement of this application with the provided literature
- The granting of a Pharmacy and Drugstore Only (PDO)-status of the product

The Board concluded that the MAH adequately has shown that the product Melatonin Tiofarma can be compared with the products as mentioned in the literature. In addition, Based on the criteria set for delivery status, the Board concluded that the PDO delivery status is acceptable.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Melatonine Tiofarma was authorised in the Netherlands on 8 October 2019.

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

LITERATURE LIST

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