CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Melatonine TioFarma 1 mg, 3 mg and 5 mg tablets
TioFarma b.v., the Netherlands

melatonin

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The applicant has checked this report for the absence of any confidential information.

Registration number in the Netherlands: not applicable

29 June 2012

Pharmacotherapeutic group:	hypnotics and sedatives
ATC code:	N05CH01
Route of administration:	oral
Therapeutic indication:	circadian rhythm disorder with delayed sleep phase in children and adults; relief of jet lag symptoms in adults
Prescription status:	prescription only
Date of authorisation in NL:	Not applicable, withdrawn by the applicant in November 2011
Application type/legal basis:	Directive 2001/83/EC, Article 10a

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) considered that the application for Melatonine TioFarma 1 mg, 3 mg and 5 mg tablets in the proposed indication of:

short-term monotherapy treatment of primary insomnia in adults

later changed to

treatment of circadian rhythm disorder associated with delayed sleep phase in children and adults, and relief of jet lag symptoms in adults

was not approvable, since "major objections" were identified. The details are provided in the report below. The applicant has responded by withdrawing the application. No marketing authorisation has been granted.

Melatonin is a naturally occurring compound found in animals, plants, and microbes. Circulating levels of melatonin vary in a daily cycle, thereby regulating the circadian rhythms of several biological functions, including the sleep/wakefulness cycle. Endogenous melatonin production diminishes with age and this is thought to contribute to impaired sleep in older individuals. Therefore it is thought that treatment with melatonin can repair age-related impaired melatonin levels thereby restoring normal sleep patterns.

A prolonged-release formulation containing 2 mg melatonin, Circadin, was registered in Europe in 2007 for the indication *short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over*. However, Circadin has been registered less than 10 years ago and legally the applicant cannot refer to this dossier for the preclinical and clinical data. Therefore the dossier of Circadin cannot be used to support the current application. The applicant changed the indication in response to comments of the MEB in which it was stated that the initial indication was not fully substantiated by the data submitted in the application.

The applicant claims that Circadin, which is an extended release product, available only in a 2 mg dose, does not meet patients' need for an immediate-release product and for different dose strengths. Although such products (*i.e.* immediate release and other dose strength) are licensed in Poland, Hungary, and in the US, the applicant claims that availability of these products in the Netherlands is poor.

Low doses of melatonin (0.1 mg) are available in the Netherlands as an over-the-counter food supplement. The maximum permitted dose under the *Warenwet* (Dutch legislation) is 0.1 mg.
Higher doses fall under the *Geneesmiddelenwet* [Dutch medicines law] and are only available with a doctor's prescription at the pharmacy as a "Magistrale Bereider" product. The indication as it appears on the KNMP [*Royal Dutch Pharmacists Association*] website is *slaapstoornissen met slechte slaapkwaliteit [sleep disorders with poor quality of sleep]*.

The applicant claims that since this formulation is commercialised as a safe and effective medication, and since melatonin has been on the market for a considerable amount of time, it can be considered as a medicinal product with a well established medicinal use according to article 10a of Directive 2001/83/EC.
This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant 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 applicant 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.

With respect to the pharmaceutical quality and pharmacokinetics, the applicant did not submit bioavailability and bioequivalence studies, but requested a biowaiver according the current guideline.

No scientific advice has been given to the applicant with respect to these products. No paediatric development programme has been submitted, as this is not required for a well-established use application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is melatonin, an established active substance however not described in the European Pharmacopoeia (Ph. Eur.)*. The active substance is a pale yellow to grayish white crystalline powder, which is freely soluble in chloroform. The drug substance is not chiral. Two polymorphic forms are reported.

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 two stages. No class 1 solvents are used. The drug substance is micronised. The active substance has been characterized by various spectral methods.
The provided information on the synthesis and control of the starting material is incomplete, the levels and control of a well known genotoxic impurity have not been provided. Additional information was requested as major objection. The specifications of the other raw materials are acceptable.

Quality control of drug substance
The drug substance specification has been established in-house. However, at the time of the withdrawal of the application many issues on the control of the drug product were not solved. Requirements for particle size distribution and individual impurities were lacking. Impurities found above the identification limit remained to be identified and specified. Results of forced degradation studies with the analytical method were not provided.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (six months). No significant changes have been observed. Loss on drying increased slightly at both storage conditions. No trends have been observed for the other parameters tested. The claimed re-test period of 2 years is considered justified. The drug substance does not need specific storage conditions.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Melatonine TioFarma 1 mg, 3 mg and 5 mg tablets are white to off white tablets, with a diameter of 6 mm, with score on one side and the other side embossed "*melatonine 1*", "*melatonine 3*" and "*melatonine 5*", respectively. 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/Aluminium blisters or polypropylene containers with LDPE cap.

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

The three strengths have the same form, size, and weight, but can be distinguished by the embossing. With the exception of the amount of active substance and the amount of lactose which is adjusted to the amount of active substance, the three strengths have the same composition.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. A direct compression approach was chosen. Development was based on a special product manufactured historically. It was optimised with regard to particle size of the drug substance and flow characteristics. Dissolution of the drug product has been compared to other immediate release melatonin products from the Polish and Hungarian market and to a prolonged release product authorised via the centralised procedure. The dissolution profile of the product at issue differs considerably from the profiles of the other melatonin products. The differences between the product at issue and the other products on the European market may have implications for the efficacy and/or safety of the product at issue. On storage, the appearance of the tablets changes to show brown spots for which the cause is unclear.

Compatibility
Results of compatibility studies between the drug substance and the excipients were missing.

Manufacturing process
The manufacturing process involves direct compression. The drug substance and excipients are mixed and the final blend is compressed. In-process controls are performed during the compression step. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data has been presented for three full-scale batches of the 1 mg and three full-scale batches of the 5 mg strength. A process validation protocol for the 3 mg strength has been provided.

Control of excipients
All excipients and components of excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, disintegration time, mean weight, hardness, friability, identification, assay, related substances, uniformity of dosage units, microbiological purity, and dissolution. The release specifications were not adjusted to be in line with observed changes in assay and impurities during storage. Impurities observed above the identification threshold were not identified nor specified. The low requirement for hardness has not been justified. The analytical methods have been adequately described. Mass balance in the results of assay and related substances was not demonstrated.

Batch analytical data from the proposed production site has been provided on three full-scale batches of the 1 mg and 5 mg strengths demonstrating compliance with the proposed release specification. Additional results have been provided of batches tested with a newly introduced method for related substances.

Stability of drug product
Stability data on the product has been provided for three full-scale batches of the 1 mg and three full scale batches of the 5 mg strength stored at 25°C/60% RH (between 18 and 24 months) and 40°C/75% RH (six months). Bracketing is applied for the 3 mg strength. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial packaging. In the available stability data, no significant changes have been observed. Decreasing trends have been observed for dissolution and hardness and increasing trends for individual and total impurities. These trends are more pronounced at accelerated conditions. In view of the uncertainty on mass balance and low hardness of the tablets, a shelf-life could not be assigned. Photostability studies demonstrated that the drug product is not photostable. The tablets should be stored in the original packaging to protect from light. Some minor pharmaceutical concerns with regard to the drug product still existed at the time of withdrawal of the application.

In-use stability
As hardness and dissolution were not included in the in-use stability studies, an in-use shelf-life has not been established.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
For lactose, a statement on compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been provided.

II.2 Non-clinical aspects

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

Pharmacology
Melatonin is an endogenous hormone. The preclinical pharmacology of melatonin has been extensively studied, and a selection of the most relevant studies has been discussed by the applicant. Melatonin is a small, lipophilic molecule that penetrates cell membranes easily. It has many effects on several of physiological functions. Some of these effects are mediated by the interaction of melatonin with its receptors. Melatonin exerts its biological effect by binding to the membrane bound ML1 (subtype 1a,1b, and 1c) and ML2 receptors. Both receptor types are located in the suprachiasmatic nucleus, whereas only ML1 receptors are found on the pituitary pars tuberalis. ML1 receptors are involved in the regulation of retinal function, circadian rhythms, and reproduction
Other non receptor-mediated effects of melatonin are suggested to be due to its chemical antioxidant properties which are seen at high and non-physiological doses.

Pharmacokinetics
The bioavailabity of melatonin is species-dependent and may be dose dependent. In many species specific melatonin binding sites have been identified widely throughout the brain with some species specificity. Approximately 90% of the produced melatonin is cleared in a single-passage through the liver either by conjugation (60%) or by oxidation (5-30%). A proportion (15-25%) of melatonin is excreted unchanged.

Toxicology

Depending on species, the route of administration and the dose given at low doses melatonin did not influence the circulating system. At (unphysiological) high doses some negative effects on vascular, motor and systemic activity were noticed. Repeated low doses did not cause severe effects but did result in body weight reduction in rats. No genotoxic, carcinotoxic, or other toxic effects were revealed in animal studies using melatonin.

Environmental risk assessment
In the environmental risk assessment the applicant states that the melatonin tablets are products, which do not contain genetically modified organisms, and thus do not contribute to an increase in the exposure of the active drug substance. Therefore, further environmental risk assessment (ERA) is not considered necessary.
An ERA is required for all applications for a marketing authorization and not only for genetically modified organisms (see guideline on the environmental risk assessment of medicinal products for human use: EMA/CHMP/SWP/4447/00). For products of well-established use the absence of data and studies could be justified by showing that no increase in the use is expected, e.g. when a shift in the market from one producer to the other is to be expected.

II.3 Clinical aspects

Literature overview
The applicant submitted a review of evidence regarding efficacy of melatonin in Jet Lag Disorder (JLD) and Delayed Sleep Phase Disorder (DSPD).

A task force of experts that was convened by the American Academy of Sleep Medicine (AASM) wrote a review of circadian rhythm sleep disorders (CRSD). The task force reviewed evidence from peer-reviewed scientific literature regarding the assessment and treatment of circadian rhythm disorders, 2084 articles were retrieved. On the basis of this evidence the task force developed recommendations related to the evaluation and therapy of CRSDs.

For Jet Lag Disorder (JLD; Sack *et al*. 2007a; CSRD Review Part I) the search identified five level 1 studies (High quality randomized controlled trial (RCT) on well-characterized subjects or patients) and 7 level 2 studies (Cohort study or flawed clinical trial (*e.g.*, small N, blinding not specified, possible non-random assignment to treatment, incompletely validated reference standards). Melatonin was administered in doses ranging from 0.5 to 10 mg, typically at local bedtime, for up to 3 days prior to departure and up to 5 days upon arrival at the destination. A variety of outcome measures were employed including subjective rating scales of jet lag symptoms, sleep logs, and standardized mood scales as well as, in a few studies, objective measures of sleep (polysomnography and modified sleep latency testing) and actigraphy and measures of functioning. In the studies that specifically examined symptoms of jet lag, 2 of the 5 level 1 studies and 4 of the 7 level 2 studies found an improvement in jet lag symptoms with melatonin.

MEB's comments:
Efficacy of melatonin on Jet Lag is difficult to estimate based on the description of these studies. This is due to the fact that:

- *Dosing schedules vary across studies both in terms of dose level and in terms of dosing time (prior to flying or only following arrival.*
- *There is variability across the studies in terms of the number of time zones that participants have flown.*
- *There is a large variability in terms of the outcome measures used in the studies. Including effects on sleep times shifts, on other sleep parameters like sleep onset and duration, on an integrated jetlag scale, and on functioning. Furthermore, there is no summary of the magnitude of effect of treatment on these different parameters and hence it is not possible to estimate whether the effects on the different parameters are clinically relevant.*

For Delayed Sleep Phase Disorder (DSPD; Sack *et al.* 2007b; CSRD Review Part II) the search identified three cross-over studies which included 8 (Dahlitz *et al.* 1991), 20 (Kayumov *et al*. 2001), and 13 (Mundey *et al.* 2005) patients respectively. The strength of melatonin in these studies varied from 0.3 mg to 5 mg and the time of administration from 1.5 hours to 6 hours before habitual bedtime. The results of these studies showed statistically significant improvement in sleep latency and in Dim Light Melatonin Onset (DLMO) and phase advance in some of the studies but no change in total sleep time or daytime alertness.

MEB's comments:
As with efficacy in jetlag, here too, the provided review does not give sufficient basis for assessing the efficacy of melatonin treatment on DSPD due to the fact that there is no consistent description of the prescribed dose and dose schedule and no information regarding the size of the effect on delayed sleep phase in terms of hours advanced or in terms of responders. This lack of information makes it impossible to assess the clinical relevance of the obtained results.

The Task force concluded (Morgenthaler *et al.* 2007) that the evidence with respect to melatonin treatment is of moderate degree of clinical certainty with respect to the treatment of DSPD and is considered as "generally accepted patient-care strategy" with respect to the treatment of Jet Lag.

MEB's comments:
The task force conclusion may be argued to have the status of treatment guideline or treatment recommendations which in turn could be used to support the WEU argument.
However, since the article was published in 2007, this does not meet the criterion of "longer than 10 years" that is stipulated in the WEU criteria. In addition, this was a US based task force and it is questionable whether EU practitioners consult such recommendations.

Another meta-analysis by Van Geijlswijk *et al.* (2010) reviewed evidence regarding the efficacy of DSPD in adults and in children and adolescents (see table 1 below). Five studies were identified for adults and four for children and adolescents. The 5 adult trials included 91 adults and the 4 paediatric trials included 226 children.

Table 1—Characteristics of placebo-controlled studies using melatonin in delayed sleep phase disorder

AUTHOR, YEAR OF PUBLICATION	QA		Baseline DLMO	Study	Melatonin	Duration,	Time of melatonin	Measures and method of data collection				
Adults	score	n	level, h:min[a]	design	dose, mg	wks	administration	DLMO	SOT	SOL	TST	WUT
Dahlitz et al. (1991)[17]	25.0	8	—	X	5	4	22:00 h		LOG	PSG	LOG	LOG
Laurant et al. (1997)[43]	26.0	25	22:35 (0:54)	X	5	2	5 h ā DLMO (mean 17:35)	PL/SAL	LOG/ACT			
Nagtegaal et al. (1998)[45]	28.5	25	23:17 (2:18)	X	5	2	5 h ā DLMO (mean 18:17)	PL	ACT	PSG		
Kayumov et al. (2001)[42]	25.0	22	—	X	5	4	19:00-22:00			PSG	PSG	
Mundey et al. (2005)[44]	19.0	11	23:46 (1:62)	P	0.3/3	4	1.5-6.5 h ā DLMO 15.00-21.30 (mean 17:15)	SAL	ACT	ACT	ACT	ACT
Children												
Smits et al. (2001)[46]	28.0	40	21:06 (1:16)	P	5	4	18:00	SAL	LOG/ACT	LOG	LOG	LOG
Smits et al. (2003)[47]	29.5	62	20:48 (0:59)	P	5	4	19:00	SAL	LOG	LOG		LOG
Weiss et al. (2006)[49]	30.0	19[b]	—	X	5	10 days	20 min ā bedtime			LOG		
van der Heijden et al. (2007)[48]	31.0	105[b]	20:34 (0:55)	P	3/6	4	19:00	SAL	ACT	ACT	ACT	ACT

[a]Data are presented as mean (SD); [b]Includes children with attention-deficit/hyperactivity disorder.
X refers to crossover studies; P, parallel-group studies; QA, quality assessment; DLMO, dim-light melatonin onset; SOT, sleep-onset time; SOL, Sleep-onset latency; TST, total sleep time; WUT, Wake-up time; SAL, saliva; PL, plasma; LOG, diary; ACT, actigraphy; PSG, polysomnography.

Of the five adults studies, three were already reviewed by the American Task Force (see above the studies by Dahlitz *et al*. 1991, Kayumov *et al*. 2001, and Munday *et al*. 2005). Of the additional 2 studies (by Laurant *et al*. 1997, and by Nagtegaal *et al.* 1998), the study by Laurent could not be found in a Pubmed search, neither is this study mentioned or discussed in the application. The study by Nagtegaal

was a crossover study with 25 patients with DSPD who were treated with 5 mg melatonin. The trial consisted of 2 subsequent periods of 2 weeks which were not separated by a washout period.

Three of the 4 paediatric studies were parallel group studies and one a crossover study.

The results of the adults and children studies are presented in table 2 below.

Table 2—Study outcomes, differentiated between studies with adults[17,42-45] and those with children[46-49] with delayed sleep phase disorder

	Adults			Children		
Outcome variable	Studies, no./ participants, no.	Mean difference (95% CI)	z score	Studies, no./ participants, no.	Mean difference (95% CI)	z score
DLMO	3/82	-1.69 h (-2.31 to -1.07)	5.34[a]	3/155	-1.13 h (-1.47 to -0.80)	6.62[a]
SOT	5/111	-0.70 h (-1.04 to -0.36)	4.08[a]	4/193	-0.64 h (-0.93 to -0.36)	4.42[a]
WUT	2/27	-0.95 h (-3,25 to 1.36)	0.8[c]	3/168	-0.16 h (-0.33 to 0.02)	1.76[c]
SOL	4/111	-30.28 min (-63.29 to 2.74)	1.80[c]	4/206	-16.04 min (-23.77 to -8.32)	4.07[a]
TST	3/67	0.77 min (-33.87 to 35.42	0.04[c]	3/168	28.39 min (13.06 to 43.72)	3.36[b]

DLMO refers to dim-light melatonin onset; SOT, sleep-onset time; WUT, wake-up time; SOL, sleep-onset latency; TST, total sleep time. [a]P < 0.0001; [b]P < 0.001; [c]Not significant

The results for the adults trials showed that melatonin treatment advanced mean Dim Light Melatonin Onset (DLMO) by 1.69 hours (95% CI: 1.07 , 2.31) and clock hour of sleep onset (SOT) by 0.70 hours (95% CI: 0.36 , 1.04).
The results for children showed that melatonin treatment advanced mean melatonin onset (DLMO) by 1.13 hours (95% CI: 0.80, 1.47) and clock hour of sleep onset by 0.64 hours (95% CI: 0.36, 0.93).

MEB's comments:
The clinical relevance of the DLMO outcome is not clear. Therefore, the sleep onset time (SOT) and wake up time (WUT) endpoints seem the most clinically relevant outcome for the indication DSPD. The other outcomes (SOL and TST) seem more relevant for the indication insomnia and less for the currently requested indication.

Advances (in adults) of 0.70 hours in sleep onset and of 0.95 hours in waking up are equal to 42 minutes (earlier falling asleep) and 57 minutes (earlier getting up).
*For children the advance is 0.64 hours, hence 38 minutes for falling asleep and 10 minutes (0.16*60) for waking up (suggesting that in children the shift is couples with increased total sleep time).*

Hence, the shift in the sleep cycle is at most an average of 1 hour in adults and ½ an hour in children.
In both cases, the clinical relevance of these results is not clear. Unfortunately, no responder analysis was presented.

Note: it may seem strange that the difference between the shift in sleep onset and the shift in waking up does not add-up to the change in total sleep time. This may be ascribed to the fact that the figures are based on different selection of studies.

Long term efficacy in children with DPSD was investigated in one study that included 33 adolescents aged 10-18 (Szeinberg *et al.* 2006). On average patients were treated for 6 month and 12 patients were treated for more than 6 month. Results were positive with respect to long-term efficacy (sleep onset time was advanced by 131 minutes, total sleep duration prolonged by 138 minutes) but safety was not reported.

MEB's comments:
These results do not provide sufficient evidence regarding long term efficacy (number is too small to reach a conclusion) or safety. No evidence for long-term efficacy in adults was provided.

A Cochrane review of the effectiveness of oral melatonin taken in different dosage regimens for alleviating jet lag after air travel across several time zones (Herxheimer and Petrie, 2009) identified 10 trials that met the inclusion criteria. All trials had a placebo comparison arm and one had in addition comparison with zolpidem. The reviewers concluded that 8 of the 10 trials found that melatonin, taken close to the target bedtime at the destination (10pm to midnight), decreased jet-lag from flights crossing five or more time zones. Daily doses of melatonin between 0.5 and 5mg were found to be similarly effective, except that people fell asleep faster and slept better after 5mg than 0.5mg. Doses above 5mg appeared to be no more effective. The relative ineffectiveness of 2mg slow-release melatonin suggests that a short-lived higher peak concentration of melatonin works better. The estimated number needed to treat (NNT) was 2, based on the only two trials that gave the necessary data. The benefit is likely to be greater the more time zones are crossed, and less for westward flights.
The authors also concluded that the timing of the melatonin dose is important: if it is taken at the wrong time, early in the day, it is liable to cause sleepiness and delay adaptation to local time.
The authors concluded that melatonin is effective in preventing or reducing jet lag, and that occasional short-term use appears to be safe. They suggest recommending it to adult travellers flying across five or more time zones, particularly in an easterly direction, and especially if they have experienced jet lag on previous journeys. Travelers crossing 2-4 time zones can also use it if necessary.
The authors further suggest that the pharmacology and toxicology of melatonin needs systematic study, and routine pharmaceutical quality control of melatonin products must be established.

MEB's comments:
With respect to the effect of melatonin on DSPD, the presented results suggest that the shift in the sleep cycle is at most an average of 1 hour in adults and ½ an hour in children. However, the clinical relevance of these effects is not clear. Responder's analysis could clarify this issue. Unfortunately, it is not certain whether the applicant can provide such an analysis, as TioFarma does not have the detailed results of the provided studies. In addition, long-term efficacy in children and in adults was not demonstrated.

With respect to the effect of melatonin of jetlag, the Cochrane review makes a convincing case for efficacy under the specified dosing schedule (i.e. taken close to the target bedtime at the destination) and for east bound flying of more than 2 time zones.

Safety
Not all studies cited include reports on safety. The review by the AASM task force does not address safety of melatonin treatment. In the meta-analysis by Van Geijlswijk *et al.* (2010), of the 5 studies that reported about safety, headache was reported in all studies. In general about 6% reported headache in the melatonin treatment groups. Other AEs included feeling cold, mood dip, decreased appetite, and dizziness.
The Cochrane review by Herxheimer and Petrie (2009) cited above concluded that The incidence of side effects was low but that case reports suggest that people with epilepsy, and patients taking warfarin (or another oral anticoagulant) should not use melatonin without medical supervision.

MEB's comments:
These results support conclusion from the previous round of assessment that although evidence from published literature is generally not sufficiently informative about safety, the conclusion that melatonin is a relatively safe medication is endorsed for adults. Nevertheless, a warning about use by people with epilepsy and those taking warfarin (or another oral anticoagulant) should be included in the product

information, if this product is approved.

Specifically with respect to safety in children, the meta-analysis of Geijlswijk *et al.* (2010) concluded that in short term (4 weeks) studies, melatonin use can be regarded as safe.

MEB's comments:
Although the evidence suggests that short-term safety in children is similar to that in adults, decreased appetite may have more consequences for children in terms of adversely affecting growth.

With respect to long-term safety, the applicant reports about an up to 3.8 years prospective follow-up study of 44 children with neurodevelopmental disabilities and treatment-resistant circadian rhythm sleep disorders who had participated in a placebo controlled, double blind cross-over trial of sustained-release melatonin (Carr *et al.* 2007). This study found no evidence of adverse reaction to melatonin therapy and no evidence for development of tolerance.
These results were confirmed by another randomized clinical study that assessed long-term melatonin treatment course, effectiveness and safety in children with attention-deficit/hyperactivity disorder and chronic sleep onset insomnia (Hoebert *et al.* 2009). The subjects of the study had participated in a randomised clinical trial on melatonin efficacy (Van Geijlswijk 2010a; Van Geijlswijk 2011).The mean follow up was 3.7 years; response rate was 94 out of 101 children. No serious adverse events or treatment related co-morbidities were reported. Sixty-five percent of the children still used melatonin daily, while temporal discontinuation of treatment resulted in a delay of sleep onset in 92% of the children. It was concluded that melatonin treatment was effective and safe on the long term.

MEB's comments:
Although not all the evidence for long-term safety comes from children in the intended indication, it would seem that long-term safety in children is adequately addressed.

Well Established Use (WEU)
Insufficient evidence is submitted to support the WEU argument.

The applicant provided sales figures of melatonin tablets since 2001 showing an increase in the number of tablets sold per year culminating in 10.5 million tablets in 2010. The applicant argues that these figures suggest a need for this product in the Dutch market.

MEB's comments:
The sales figures do not provide any knowledge about the indications for which melatonin was used and therefore do not address the need to demonstrate well established use in the requested indication.

With respect to DSPD and Jet Lag in adults, the applicant argued that melatonin has been recommended for use by the US task force of experts that was convened by the American Academy of Sleep Medicine (AASM) and the recommendation of this task force as summarized by Morgenthaler *et al.* (2007).

***MEB's comments*:**
Even if the recommendation by Morgenthaler et al. (2007) could be viewed as a guideline, it would be mostly directed to US rather than to EU practitioners. Furthermore, the WEU directive (2001/83/EC) indicates the need to document at least 10 years of systematic and documented use in the requested indication while the article of Morgenthaler is from 2007 and hence less than 10 years ago.

Therefore it is concluded that WEU of melatonin was not demonstrated.

With respect to children and adolescents, the applicant argued that in the Netherlands, the use of 1 mg melatonin as immediate release dose form has been recommended for the treatment of sleep disorders in children in the *Kinderformularium* [Dutch formulary for children]. It is claimed that in this *Kinderformularium* it is stated that melatonin use is sufficiently investigated for the treatment of sleep disorders in children suffering from attention-deficit hyperactivity disorder, mental retardation or visual handicap. It is recommended to commence treatment with a starting dose of 1 to 2 mg administrated orally per day.

Depending on effect, dose may be increased to maintenance dose of 3 mg orally once a day for children < 40 kg and 6 mg orally once a day for children ≥ 40 kg. In the *Kinderformularium* available application formulas are listed. The melatonin 1 mg tablet (immediate release) is delivered by a sister company of the applicant. The applicant claims that this product is essentially equal to the product under consideration in qualitative and quantitative composition, and production process.
In addition, in the British National Formulary for children, melatonin is indicated for the treatment of sleep onset insomnia and delayed sleep phase syndrome, a somewhat broader indication with respect to the Dutch formulary. Prescribed dosing scheme: by mouth; child 1 month to 18 years initially 2-3 mg daily before bedtime increased if necessary after 1-2 weeks to 4-6 mg before bedtime; max. 10 mg daily.

MEB's comments:
The indication listed for Circadin in the Kinderformularium under melatonin (http://www.kinderformularium.nl/search/stof.php?id=322 is "slaapstoornissen" [sleep disorders] and not circadian rhythm disorder or delayed sleep phase disorder. Therefore there seems no basis for the claim of WEU of melatonin for the requested indication in children.

Benefit-risk assessment
Based on the published literature, efficacy of melatonin treatment for jet lag seems moderately convincing provided that a specified dosing schedule is followed, *i.e.* if it is taken close to the target bedtime at the destination and for east bound flying of more than 2 time zones.

However, for DSPD the results suggest that the shift in the sleep cycle is at most an average of 1 hour in adults and ½ an hour in children. The clinical relevance of these results is not clear and, unfortunately, no responder analysis was presented to support clinical relevance. In addition, long-term efficacy was not demonstrated.

As was concluded in a previous assessment round, safety seems acceptable.

Therefore it is concluded that the benefit/risk for jetlag can be considered moderately positive and that for DSPD efficacy is uncertain, as clinical relevance of the obtained results is not established. In addition, long term efficacy was not demonstrated.

Overall, Melatonine TioFarma 1 mg, 3 mg and 5 mg tablets are not approvable for the requested indications, since major objections have been identified, which preclude a recommendation for marketing authorisation at the present time.

Major objections:
- Well-established use was not demonstrated.
  - Even if the recommendation by Morgenthaler *et al.* (2007) could be viewed as a guideline, it would be mostly directed to US rather than to EU practitioners. Furthermore, the WEU directive (2001/83/EC) indicates the need to document at least 10 years of systematic and documented use in the requested indication while the article of Morgenthaler is from 2007 and hence less than 10 years ago.
  - The sales figures do not provide any knowledge about the indications for which melatonin was used and therefore do not address the need to demonstrate well-established use in the requested indication.
  - The *Kinderformularium* lists under melatonin only Circadin, an extended-release melatonin formulation. Furthermore, the indication listed for Circadin in the document is "slaapstoornissen" [*sleep disorders*] and not circadian rhythm disorder or delayed sleep phase disorder. Therefore there seems no basis for the claim of WEU of melatonin for the requested indication in children.

- Information on the levels and control of a well known, genotoxic impurity still needs to be provided.

Other concerns not solved at the time of application:
- There remain many other points on quality that still need to be resolved.

- Efficacy results for DSPD suggest that the shift in the sleep cycle is at most an average of 1 hour in adults and ½ an hour in children. The clinical relevance of these results is questionable. Unfortunately, no responder analysis was presented. The applicant is requested to address the clinical relevance of the effect of treatment on DSPD in children and in adults. In addition, long-term efficacy was not demonstrated.
- The pharmacovigilance system is endorsed, however, the applicant should submit information on a validated database for case reports within three months in agreement with more strict criteria set for the pharmacovigilance database shortly. Therefore, a validated database was requested.

Risk management plan

Upon studies with another melatonin product, Circadin, a Risk management plan (RMP) has been constituted. The RMP of that product should not be duplicated, but should be followed, where appropriate.

The applicant already committed to the following issues:

- The following issues should be monitored and specifically reported upon in the PSURs:
  - Thyroid disorders, Retinal effects, Nightmares, Suicide attempt/suicidal Ideation/mood disturbance, Hypopotassaemia, Psychotic Disorder, Chest pressure, Anaphylactic reactions/Allergic reactions, Panic attacks, Confusion, Hallucinations, Potential interaction with warfarin and effects on clotting, Withdrawal.
  - Loss of consciousness, Infections
  - Off-label use, Use in pregnancy/lactation
- The SPC for the product should follow and be kept in line with that of Circadin.
- The applicant should follow, where appropriate, the risk minimisation activities of Circadin

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The MEB, on the basis of the data submitted, considered that for Melatonine TioFarma 1 mg, 3 mg and 5 mg tablets well-established use has not been demonstrated. Furthermore, demonstration of efficacy was insufficient (see also discussion below). In reaction to this, the applicant has withdrawn the application. Therefore, the procedure was finalised and no marketing authorisation was granted.

Melatonine TioFarma is intented for treatment of circadian rhythm disorder associated with delayed sleep phase in children and adults, and relief of jet lag symptoms in adults. The application was based on the well-established use of melatonin.

The following major deficiencies were noted in the application:

- Objections raised with regard to the chemical-pharmaceutical quality of the product have not yet been resolved.
- Based on the data provided, at least 10 years of systematic and documented use in the requested indication is not considered proven.
- The clinical relevance of the results obtained in DSPD as described in the literature is questionable, and no responder analysis was presented to support clinical relevance. In addition, long-term efficacy was not demonstrated.

In the Board meeting of 29 July 2010, the application was discussed. The Board's conclusion was that the presented dossier does not demonstrate well-established use of melatonin in the sought indications. The national procedure was finalised after the applicant's withdrawal in November 2011.

List of abbreviations

AASM	American Academy of Sleep Medicine
AE	Adverse Event
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
DHPC	Direct Healthcare Professional Communication
DSPD	Delayed Sleep Phase Disorder
DLMO	Dim Light Melatonin Onset
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
JLD	Jet Lag Disorder
KNMP	Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie [*Royal Dutch Pharmacists Association]*
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
NNT	Number Needed to Treat
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
RCT	Randomized Controlled Trial
SD	Standard Deviation
SOT	Sleep Onset Time
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States
WEU	Well-established Use

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