COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Melatonine Owlpharma 2 mg, film-coated tablets

(melatonin)

NL/H/5041/001/DC

Date: 18 January 2021

This module reflects the scientific discussion for the approval of Melatonine Owlpharma 2 mg, film-coated tablets. The procedure was finalised at 30 September 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Melatonine Owlpharma 2 mg, film-coated tablets, from Owlpharma Consulting, LDA.

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

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

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

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

The active substance melatonin has been used in the community (specifically Hungary and Denmark) for more than 10 years for the indication jet lag. 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 concerned member states (CMS) involved in this procedure were Denmark, Norway and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Melatonine Owlpharma is a white/off-white to beige, biconvex, circular shaped film-coated tablet with a score line and "2" on one side. Each film-coated tablet contains 2 mg melatonin. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The film-coated tablets are packed in HDPE tablet container (white polyethylene bottle) with HPDE/LDPE closure containing desiccant.

The excipients are: microcrystalline cellulose (E460), maltodextrin, colloidal anhydrous silica (E551), magnesium stearate (E470b), croscarmellose sodium (E468) and hypromellose (E464).

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 soluble in acetone, ethyl acetate and methanol. The drug substance does not exhibit polymorphism and does not show 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 MAH or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The synthetic route consists of one synthetic and one purification step or four steps (depending on manufacturer). No class-I solvents or metal catalysts are used in the synthesis. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The active substance specification of the MAH is in line with the specification of the ASMF-holder with an additional test for microbiological quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three full-scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for several production and pilot scaled batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). No significant changes or trends have been observed. The claimed re-test period of 5 years has been justified when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. During development, dissolution testing is used to investigate the amount of croscarmellose sodium and upscaling. The dissolution method development has been adequately described and the choices made were justified. For this well-established use application bridging based on comparative *in vitro* dissolution studies at pH levels of 1.2, 4.5 and 6.8 vs to the a representative product for the most commonly used products in literature, is performed. The *in vitro* dissolution results demonstrate similar dissolution profiles in pH 1.2, 4.5 and 6.8 media.. For the final conclusion on the suitability of the reference product and supportive bridging data, reference is made to the clinical aspects. The formulation of the melatonin 2 mg film-coated tablets is based on the already developed in-house melatonin 3 mg film-coated tablets. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process involves mixing, blending, compression and coating. The process is described in sufficient detail and has been validated according to relevant European guidelines. It is considered a non-standard process due to low content of active substance. Process validation data on the product have been presented for three full-scaled batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph. Eur. requirements. The proposed specifications are acceptable.

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 dosage units, identification, dissolution, related substances, assay, microbial quality and loss

on drying. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life requirements are identical. Satisfactory validation data for the analytical methods have been provided. Batch analytical data for three full-scaled 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 commercial batches stored at 25°C/60% RH (6 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. A photostability study showed that the product is sensitive to light. On basis of the data submitted, a shelf life was granted of 2 years. The labelled storage conditions are "This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture."

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 Owlpharma has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

No non-clinical studies have been performed by the MAH. Extensive preclinical tests concerning pharmacology and toxicology have been described in the literature. The MAH selected the most relevant studies/reviews which are used in the non-clinical overview to support this application. Since melatonin can be regarded as a well known substance it is agreed that a non-clinical overview based on literature review is appropriate and no additional studies are required from the MAH.

III.2 Pharmacology

Melatonin is the main hormone secreted by the pineal gland. It serves a time-keeping function in various species. Melatonin regulates circadian rhythm that is governed by the central circadian pacemaker in suprachiasmatic nucleus of the hypothalamus. Melatonin has

a hypnotic/sedative effect on cognition when given orally. Melatonin regulates circadian rhythms such as the sleep wake rhythm, neuroendocrine rhythms or body temperature cycles through its action on MT1 and MT2 receptors. *In vitro* and *in vivo* studies in various animal species demonstrated the effect of melatonin on sleep and circadian rhythm regulation. In addition, melatonin demonstrated anxiolytic, analgesic, antioxidant, anti-tumour, anticonvulsant and motor effects as well. Melatonin prevented the well-recognised increase in glucose levels that usually follows exposure to insulin.

III.3 Pharmacokinetics

Melatonin is rapidly and extensively absorbed and low first-pass hepatic extraction in rats after oral administration. The mean oral bioavailability of a 10 mg/kg dose of melatonin was found to be 53.5% in rats, while values exceeding 100% were obtained in dogs and monkeys. Melatonin is moderately distributed in rats, dog and monkeys. Melatonin accounted for only 35 to 50% of the total radioactivity in most tissues. Melatonin is metabolised primarily in the liver. A major metabolite of melatonin in rodents and man is aMT6S. Apparent elimination half-life of melatonin following an intravenous dose of 3 mg/kg was 19.8, 18.6, and 34.2 min, respectively, in rats, dogs, and monkeys. The total radioactivity found in the urine during this time accounted for 60 to 70% of the administered melatonin and about 15% of the administered radioactivity was found in the faeces. 5-methoxypsoralen impaired the 6-melatonin hydroxylation at pharmacologically relevant concentrations. Diazepam, tamoxifen and acetaminophen (paracetamol) demonstrated impairment in the metabolic conversion of melatonin to 6-sulphatoxymelatonin in animals however, those drugs did not impair metabolic conversion at concentrations attained following therapeutic administration in humans.

III.4 Toxicology

Single dose toxicity studies performed in rat and mice revealed no special hazard for humans. Large doses (up to ≥200 mg/kg) of melatonin caused similar behavioural effects in mice and rat. Repeat dose toxicity studies in mice showed life prolongation of dark-cycle melatonin-treated animals when compared with controls. Melatonin supplementation (16 months) markedly increased the number of rats which survived to the age of 27-29 months *In vitro* and *in vivo* genotoxicity studies demonstrated that melatonin is not genotoxic. Carcinogenicity studies suggested that carcinogenic liability of melatonin in humans is low. The no-observed-adverse-effect-level and lowest-observed-adverse-effect level for maternal toxicity were 100 and 200 mg/kg/day (which is approximately 833 and 1667 times of the maximum recommended human dose), respectively. In rats, the no-observed-adverse-effect-level was ≥ 200 mg/kg/day in developmental toxicity which is approximately 1667 times of maximum recommended human dose. In two postnatal development studies in rats and squirrels, melatonin treatment caused delay in sexual maturation. These data indicate that exogenous melatonin crosses placenta and is secreted in milk, and it may influence the ontogeny and activation of the hypothalamic-pituitary-gonadal axis. Thus, pre-clinical data of melatonin has no special hazard for humans based on conventional studies of single-dose

toxicity, repeated-dose toxicity, genotoxicity, and carcinogenicity, and reproductive and developmental toxicity.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Melatonin tablets are to be used as a substitute for similar melatonin containing products with comparable strength and the same indication and use. The product will therefore not contribute to an increase in environmental exposure. Therefore, melatonin is not expected to pose a risk to the environment and an ERA is not warranted.

III.6 Discussion on the non-clinical aspects

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

IV. CLINICAL ASPECTS

IV.1 Introduction

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

IV.2 Pharmacokinetics

Oral administration of melatonin is complete with high inter-individual variability. Mean bioavailability of oral melatonin is approximately 15%. Poor bioavailability is due to high first-pass metabolism. Presence of food can increase the melatonin exposure almost two fold. However, the increased AUC in the fed state is unlikely to be of clinical significance, particularly in view of the large inter-individual variations. However in the SmPC, it has been mentioned that food is not consumed approximately 2 hours before and 2 hours after intake of melatonin. Melatonin shows dose-proportional pharmacokinetics.
Melatonin is approximately 60% bound with plasma protein. Melatonin distributes from serum to saliva as well as albumin-bound melatonin crosses the blood-brain barrier. Isozymes CYP1A1, CYP1A2 and CYP2C19 of the cytochrome P450 system are involved in the hepatic metabolism of melatonin. Melatonin is converted to 6-hydroxymelatonin by the liver. The principal metabolite is 6-sulphatoxy-melatonin, which is inactive. The $t_{½}$ is about 45 minutes. Elimination of metabolites occurs mainly by renal excretion, about 90% being

excreted as sulphate and glucuronide conjugates of 6-hydroxy-melatonin. These are adequately reflected in the MAH SmPC.
Cytochrome P450 isoenzymes CYP1A1 and CYP1A2 are involved in the metabolism of melatonin and consequently other drugs that inhibit or induce these isoenzymes may affect melatonin levels. Melatonin should not be taken with fluvoxamine, methoxsalen, cimetidine, or oestrogens, all of which increase melatonin concentrations through inhibition of its metabolism. Tobacco smoking has been reported to decrease melatonin concentrations. These are adequately reflected in the MAH SmPC.

IV.3 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. Other mechanisms of action, including those that do not involve the MT1 and MT2 receptors, can not be excluded.

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

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

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

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

IV.4 Clinical efficacy

Altogether 10 controlled studies are presented in support of the jet lag indication. All studies examined healthy volunteers. Some were accustomed to international flight and had experienced discomfort after an eastward trip. Study participants were recruited from diverse segments of the population such as visitors to a university travel clinic, physicians, university and airport staff, medical personnel, sports officials, scientists and airline cabin crews. Therefore, the overall study population is considered representative of intercontinental flight passengers. In addition, participant age ranged from the mid twenties to mid sixties in most studies, and reasons for travel included work and leisure.

Studies were generally small, including 10-15 patients per arm (the studies by Arendt 1987, Arendt & Aldhous 1988, Petrie 1989, Claustrat 1992, Petrie 1993, Nickelsen 1991, Edwards 2000,) 3 studies included around 60 subjects per arm (Suhner 1998 and Spitzer 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 melatonin (i.e. 0.5 mg in the studies by Suhner 1998a and in Spitzer 1999) suggest that such low doses are not effective and a higher than 5 mg dose is not clearly more effective (8 mg dose studied in study by Claustrat 1992). 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 2 or 3 mg may be preferable to start with. Therefore recommending 2 mg with a possibility to increase to 6 mg, as in the proposed posology, is supported by the evidence.

Timing of intake, i.e. at habitual bedtime at destination is supported. Individual variations in melatonin metabolism exist, there is no strong basis to recommend exact timing.
Duration of treatment of 5 days is consistent with the evidence and is therefore accepted. The limitation to a maximum of 16 treatment periods per year limits the theoretical continuous exposure to 80 days, corresponding to <3 months, which is considered acceptable taking into account that large meta-analyses pooling data from melatonin trials performed in primary and secondary sleeping disorders showing that short-term use i.e. <3 months is in general safe.

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

Nine of the ten studies demonstrated statistically significant effects on jet lag symptoms or sleep. With respect to clinical relevance: two of the studies conducted a responders analysis (Arendt 1987 and Calustrat 1992) with respect to self assessed jet lag severity and both

showed a considerable difference (67% and 40%, respectively) in % responders. A study (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.

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

Altogether, it is considered that nine out of ten studies demonstrated statistically significant effects on jet lag symptoms (e.g. mood, cognitive) or on sleep (which is perhaps the most important jet lag symptom) and that two out of ten studies with results for responders analysis concerning global jet lag symptoms (Arendt 1987 and Calustrat 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 and Petrie, 2002, reviewed 2008), which concluded that melatonin (0.5 to 5 mg/day) is effective in preventing or reducing jet lag.

IV.5 Clinical safety

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

The available evidence suggests that administration of exogenous melatonin during the day can alter the timing of the diurnal secretory patterns of other hormones, e.g. those involved in reproductive system. Typical therapeutic doses of melatonin seem to have, at most, a slight, transient effects on the level of other hormones.

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 proposed SmPC.

Secondary pharmacology of melatonin suggests 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 MAH proposes a warning text for section 4.4 of the SmPC indicating that melatonin is not recommended in patients with autoimmune diseases, which is accepted.

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

In addition, the evidence submitted suggests 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 proposed SmPC advices not to use melatonin in children, due to lack of evidence in children and the fact that it is unknown to what extent exogenous melatonin modulates gonadal axis pre-puberty in humans. This is accepted.

Altogether, the (limited) 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 Owlpharma.

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

Important identified risks	None
Important potential risks	- Off-label use in paediatric patients with sleep disorders
Missing information	- Use in patients with renal or hepatic impairment - Use in patients with autoimmune disorders - Fertility, 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. Limitation of the pack size to 30 tablets as a risk minimisation measure has been adopted to prevent off-label use of melatonin.

IV.7 Discussion on the clinical aspects

Altogether it is considered that efficacy of melatonin in the treatment of jet lag has been established as the majority of studies in jet lag subjects showed statistically significant and clinically relevant results. In addition, the safety of melatonin is considered generally benign

and it is considered that the safety issues that are identified and are adequately addressed in the SmPC.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report. 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 Owlpharma 2 mg, film-coated tablets has a proven chemical-pharmaceutical quality in view of the present European regulatory requirements. The efficacy has been demonstrated for the indication jet lag in adults and the safety issues that were identified are adequately addressed by SmPC warnings and the Risk Management Plan. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member state, on the basis of the data submitted, considered that well-established use has been demonstrated for Melatonine Owlpharma and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 September 2020.

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

Arendt J, M Aldhous, J English, V Marks, JH Arendt, M Marks & S Folkard. Some effects of jet-lag and their alleviation by melatonin. Ergonomics 1987; 30(9): 1379-1393

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Petrie K, Conaglen JV, Thompson L, Chamberlain K. Effect of melatonin on jet lag after long haul flights. Br Med J 1989; 298: 705-707

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Spitzer RL, Terman M, Williams JBW, et al. Jet lag: Clinical features, validation of a new syndrome-specific scale, and lack of response to melatonin in a randomized, double-blind trial. Am J Psychiatry 1999; 156: 1392–1396

Suhner A, Schlagenhauf P, Johnson R, Tschopp A, Steffen R. Comparative study to determine the optimal melatonin dosage form fort he alleviation of jet lag. Chronobiology International 1998; 15(6): 655-666