Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Melatonin 2 mg Hard Capsules
Melatonin 3 mg Hard Capsules

melatonin

PL 55612/0077 – 0078

ENNOGEN IP LTD

LAY SUMMARY

Melatonin 2 mg and 3 mg Hard Capsules
melatonin

This is a summary of the Public Assessment Report (PAR) for Melatonin 2 mg and 3 mg Hard Capsules. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Melatonin in this lay summary for ease of reading.

For practical information about using Melatonin, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Melatonin and what is it used for?
These applications are for medicines that have a well-established use. This means that the use of the active substance in the medicines has been well-established in the UK/European Union for at least 10 years, with recognised efficacy and an acceptable level of safety.

Melatonin can be used for treatment of jet lag in adults. Jet lag can be recognised by sleep disturbances, daytime tiredness, fatigue, mild mental impairment, irritability and digestive system disturbances experienced after flying.

How does Melatonin work?
Melatonin is a hormone produced by the body that synchronises the body's biological day-and-night rhythm. The biological rhythm can be disturbed by travelling across time zones. This is known as jet lag. The symptoms and their severity vary between individuals but are generally worse and last longer the more time zones are crossed. Melatonin can help restore the normal day-and-night rhythm and reduce the symptoms.

How is Melatonin used?
The pharmaceutical form of these medicines is hard capsules, and the route of administration is oral (by mouth).

Patients should talk to a doctor if they do not feel better or feel worse after 5 days.

The first dose should be taken on arrival at destination at the habitual bedtime. Intake on the following days should also be at the habitual bedtime. The capsules should not be taken before 20:00 hr or after 04:00 hr.

The capsules should be swallowed whole with water or other liquid (e.g. milk, fruit juice). Food should not be consumed 2 hours before or 2 hours after intake of Melatonin. Melatonin may be taken for a maximum of 16 treatment periods per year.

<u>Melatonin 2 mg and 3 mg Hard capsules</u>
The recommended dose for adults, including the elderly, is 3 mg daily for a maximum of 5 days. The dose may be increased to 5 mg or 6 mg (2 capsules of 3 mg taken simultaneously) when the effect of Melatonin is inadequate. A lower dose of 2 mg may be sufficient for some individuals.

For further information on how Melatonin is used, refer to the PILs and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Melatonin have been shown in studies?
As the active substance Melatonin has been in clinical use for over 10 years, data were provided in the form of literature references to show that Melatonin is a safe and efficacious treatment for the treatment of jet-lag in adults.

What are the possible side effects of Melatonin?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Melatonin approved?
It was concluded that the data provided from literature references had shown that Melatonin is effective in the treatment of jet-lag in adults.
Furthermore, the well-established use of the active substance Melatonin has shown that it has a recognised efficacy and an acceptable level of safety. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Melatonin?
A Risk Management Plan (RMP) has been developed to ensure that Melatonin is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

The RMP details the important risks of Melatonin, how these risks can be minimised, any uncertainties about Melatonin (missing information), and how more information will be obtained about the important risks and uncertainties.

There are no safety concerns associated with use of Melatonin.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Melatonin

Marketing Authorisations were granted were granted in the United Kingdom (UK) for Melatonin 2 mg and 3 mg Hard Capsules, (PL 40739/0271- 0272) to Ennogen Healthcare Limited on 7 June 2024. Subsequent to Change of Ownership (COA) procedures, the Marketing Authorisations were transferred to the Marketing Authorisation Holder (MAH), Ennogen IP Limited on 29 August 2024 as PL 55612/0077– 0078.

The full PAR for Melatonin follows this summary.

This summary was last updated in March 2025.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Melatonin 2 mg and 3 mg Hard Capsules (PL 55612/0077 – 0078) could be approved.

The products are approved for short-term treatment of jet lag in adults.

The name of the active substance is melatonin. Melatonin is a hormone. Melatonin secreted by the pineal gland is involved in the synchronisation of circadian rhythms to the diurnal light-dark cycle. Melatonin secretion/plasma melatonin level increases shortly after the onset of darkness, peaks around 02:00 – 04:00 hr and declines to the daytime nadir by dawn. Peak melatonin secretion is almost diametrically opposite peak daylight intensity, with daylight being the primary stimulus for maintaining the circadian rhythmicity of melatonin secretion.

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

These applications were approved under Regulation 54 of The Human Medicines Regulation 2012, as amended (previously Article 10a of Directive 2001/83/EC, as amended), as well-established use applications. No new non-clinical or clinical studies were submitted, as the data submitted for these applications is in the form of literature references.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

National marketing authorisations was granted in the United Kingdom (UK) Melatonin 2 mg and 3 mg Hard Capsules (PL 40739/0271 - 0272) to Ennogen Healthcare Limited on 7 June 2024.

Subsequent to Change of Ownership (COA) procedures, the Marketing Authorisations were transferred to the Marketing Authorisation Holder (MAH), Ennogen IP Limited on 29 August 2024 as PL 55612/0077 – 0078.

II QUALITY ASPECTS

II.1 Introduction

These products consist of:

- Hard capsules containing 2mg of melatonin (PL 55612/0077)
- Hard capsules containing 3 mg of melatonin (PL 55612/0078)

In addition to melatonin, these products also contain the excipients cellulose microcrystalline, colloidal anhydrous silica and magnesium stearate in the tablet core. The below excipients are specific to each product:

Melatonin 2 mg Hard Capsules

- Capsule shell - brilliant blue, yellow iron oxide, azorubine, black iron oxide, titanium dioxide (E171), polyethylene glycol 4000, water, gelatin.
- Printing ink - shellac (E904), potassium hydroxide, black iron oxide (E172).

Melatonin 3 mg Hard Capsules

- Capsule shell - brilliant blue, yellow iron oxide, ponceau 4R, black iron oxide, titanium dioxide (E171), polyethylene glycol 4000, water, gelatin.
- Printing ink - shellac (E904), potassium hydroxide, black iron oxide (E172).

The finished products are packaged in PVC/PE/PVDC blister packs. Melatonin 2 mg and 3 mg Hard Capsules are presented in packs of 10, 14, 28 and 30 capsules. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

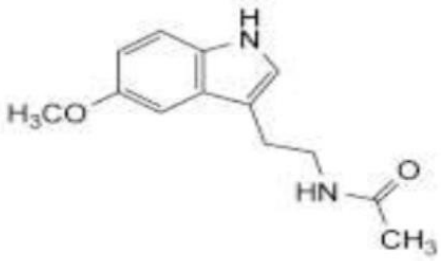
II.2 ACTIVE SUBSTANCE

rINN: melatonin

Chemical Name: *N*-Acetyl-5-methoxytriptamine; *N*-[2-(5-methoxy-1*H*-indol-3-yl) ethyl]acetamide

Molecular Formula: $C_{13}H_{16}N_2O_2$

Chemical Structure:



Molecular Weight: 232.3

Appearance: A white to off-white crystalline powder.

Solubility: Slightly soluble in water; soluble in acetone, ethyl acetate and methanol.

The information related to the active substance was provided in an ASMF. The Active substance is the subject of a Ph.Eur. monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished products.

These products do not contain or consist of genetically modified organisms (GMO).

Manufacture of the products

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years with the storage conditions ‘Store below 30°C. Store in

the original package to protect from light.'. Store in the original package to protect from light.', is acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

These applications were submitted under Regulation 54 of The Human Medicines Regulation 2012, as amended, as well-established use applications. No new non-clinical studies were submitted, as the data submitted for these applications is in the form of literature references. The literature review provided is satisfactory.

III.2 Pharmacology

Melatonin is an endogenous molecule produced in the human vertebrate pineal gland, the retina and possibly in some other organs. It displays a marked circadian rhythm, with high levels at night and low levels during the day. Exogenous melatonin has the same action, which can be labelled as "chronobiotic". The pharmacological mechanism of action in melatonin is believed to be based on its interaction with MT1-, MT2- and MT3 receptors, as these receptors (particularly MT1 and MT2) are involved in the regulation of sleep and circadian rhythms in general.

Melatonin or N-acetyl-5-methoxytryptamine, identified in 1958, is a hormone produced and secreted by the pineal gland in the brain. Melatonin is synthesized from serotonin via two enzymes: serotonin-N-Acetyl Transferase (AANAT), which converts serotonin into N-acetyl-serotonin, a key enzyme kinetically limiting the synthesis of melatonin, and Acetyl-serotonin-methyltransferase (ASMT), which produces the final conversion into melatonin. This secretion is essentially nocturnal, whilst during the day melatonin is almost undetectable. Nocturnal levels are thus ten times higher than those in the daytime, bearing in mind that the inter-individual variability of melatonin secretion is substantial. This hormone has many physiological functions, the main function being to synchronise an individual's biological rhythms in response to photoperiods, i.e. day/night cycles.

Exogenous melatonin has the same action, which can be labelled as "chronobiotic", from very low doses (0.125 mg). A chronobiotic substance can change the characteristics of a rhythm (period, amplitude or phase). Exogenous melatonin influences the functioning of the biological clock (suprachiasmatic nuclei), which responds by an advance or delay, according to the time of administration When melatonin is administered in the afternoon (beginning and end), an advance in all biological rhythms is observed, with a maximum effect when melatonin is taken 4 to 5 hours before the start of the endogenous secretion. This effect is used for the treatment of delayed sleep phase syndrome. When melatonin is administered in the morning, a delay in biological rhythms is observed, which has a particular influence on the sleep-wake cycle. Furthermore, melatonin has a promoter effect on sleep and this action can be called "soporific" occurring in a dose-effect relationship, i.e. increasing with the dose. The increase in dose of melatonin is accompanied by an increase in the soporific effect, but probably with similar chronobiotic effects.

III.3 Pharmacokinetics

Exogenously administered melatonin is well-absorbed following oral administration. It is widely distributed to tissues and readily penetrates the blood-brain barrier. Melatonin was also shown to cross the placental barrier. Melatonin is rapidly and primarily metabolised by the liver and cleared from the body. The major metabolic pathway determined in humans, mice, rats and rabbits involves 6-hydroxylation in the liver via the hepatic microsome P-450 system to yield 6-hydroxymelatonin. CYP1A2 is a major catalyst of the 6-hydroxylation of melatonin. The main excretion route of the melatonin metabolites is renal.

III.4 Toxicology

Melatonin has a low toxicity after single administration. In repeat-dose toxicity (rats and dog) effects on the liver (hypertrophy) and genital tract of male rats and female dogs were observe at exposure in large excess of the intended human exposure at therapeutic dose. In reproductive studies, melatonin induced some toxicological effects on the embryo-foetal development in rabbits and on the postnatal developmental in rats. The incidence of pituitary adenomas and thyroid follicular cell adenomas was increased in males in the rat carcinogenicity study. The genotoxicity profile of melatonin was negative. The data suggest the carcinogenic liability of melatonin in humans is low.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the applications are for products containing an active substance of well-established use that will be used in place of existing products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects

An adequate review of the available published data on the non-clinical pharmacology, pharmacokinetics and toxicology has been provided. The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

No new clinical studies were submitted, as the data submitted for these applications is in the form of literature references. The literature review provided is satisfactory.

The applicant has identified a licensed medicinal product for the purpose of bridging the proposed product to the bibliographic data. This is acceptable.

The bridging product (BioMelatonin 3mg film-coated tablet, approved in the UK in 2022 as Syncrodin 3mg film coated tablet) is an immediate release, oral, solid dosage form indicated for the short-term treatment of jet lag in adults. The bridging product is considered to be representative of the use of melatonin in the short-term treatment of jet lag in adults. The quality assessment has concluded pharmaceutical equivalence between the proposed product and the bridging product.

Eleven clinical trials are described that investigated the effectiveness and safety of melatonin in the treatment of jet lag and were published between 1987 – 2004 – reflecting the longstanding scientific interest in the potential use of melatonin to alleviate symptoms of jet lag. All the clinical trials investigating jet lag were either placebo controlled or included an

active comparator. More recent clinical trials have also been conducted, as well as a number of systematic reviews of melatonin in sleep disturbance, including jet lag; these include a review of ten clinical trials that specifically investigated the effect of melatonin treatment on jet lag. Melatonin at doses of between 0.5 mg and 8 mg against either a placebo or a short acting hypnotic were included. A dose of 5 mg was more effective than 0.5 mg but there was no gain from doses higher than 5 mg. The conclusion from the review was that melatonin in short term use is safe and effective in reducing the symptoms of jet lag. Two additional systematic reviews that investigated use of melatonin in jet lag also concluded a clinically relevant effect.

The published evidence points to sustained release formulations of melatonin being less effective than immediate release formulations for the treatment of jet lag; however, sustained release formulations may be advantageous in other types of sleep disturbance. Provided the dose recommendations for the proposed product are adhered to, in respect of timing and the maximum recommended dose of 6 mg for up to a maximum of 5 days, the safety profile is favorable. Drowsiness and reduced alertness are the main risks. Warnings are in place in the product information in regard to driving and operating machinery.

IV. 2 Pharmacokinetics

Melatonin is a small, amphiphilic molecule (molecular weight 232 g/mol) active in its parent form. Melatonin is synthesised in the human body from tryptophan via serotonin. Small quantities are obtained via diet. Data summarised below are from studies that generally involved healthy men and women, primarily young and middle-aged adults.

Absorption

Orally administered melatonin is almost completely absorbed. Oral bioavailability is ~ 15%, owing to first-pass metabolism of ~ 85%. Plasma T_{max} is ~ 50 minutes. A 3 mg dose of immediate-release melatonin raises plasma melatonin C_{max} to ~ 3400 pg/mL, which is ~ 60-times the nocturnal (endogenous) plasma melatonin C_{max}, though both endogenous- and exogenous C_{max} show considerable inter-individual variation.

Data on the effect of intake of food at or around the time of intake of melatonin on its pharmacokinetics are limited, though suggest that concomitant food intake may increase absorption almost 2-fold. Food appears to have a limited effect on T_{max} for immediate-release melatonin. This is not expected to affect the efficacy or safety of Melatonin Hard Capsules; however, it is recommended that food is not consumed approximately 2 h before and 2 h after intake of melatonin.

Distribution

The protein binding of melatonin is approximately 50 – 60%. Melatonin primarily binds to albumin, though also binds alpha1-acid glycoprotein; binding to other plasma proteins is limited. Melatonin rapidly distributes from the plasma into and out of most tissues and organs and readily crosses the brain-blood barrier. Melatonin readily crosses the placenta. The level in umbilical blood of full-term babies closely correlates with and is only slightly lower (~ 15 – 35%) than that of their mother following ingestion of a 3 mg dose.

Biotransformation

Melatonin is mainly metabolised by the liver. Experimental data suggest that the cytochrome P450 enzymes CYP1A1 and CYP1A2 are primarily responsible for melatonin metabolism,

with CYP2C19 of minor importance. Melatonin is primarily metabolised to 6-hydroxymelatonin (constituting ~ 80 – 90% of melatonin metabolites recovered in the urine). N-acetylserotonin appears to be the primary minor metabolite (constituting ~ 10% of melatonin metabolites recovered in the urine). Melatonin metabolism is very rapid, with plasma 6-hydroxymelatonin level rising within minutes of exogenous melatonin entering the systemic circulation. 6-hydroxymelatonin undergoes sulfate conjugation (~ 70%) and glucuronide conjugation (~ 30%) prior to excretion.

Elimination

Plasma elimination half-life ($T_{½}$) is ~ 45 minutes (normal range ~ 30 – 60 minutes) in healthy adults. Melatonin metabolites are mainly eliminated by the urine, ~ 90% as sulfate and glucuronide conjugates of 6-hydroxymelatonin. Less than ~ 1% of a melatonin dose is excreted unchanged in urine.

Linearity

Plasma melatonin C_{max} and AUC increase in a directly proportional, linear manner for oral doses of immediate-release melatonin in the range 3 – 6 mg whereas T_{max} and plasma $T_{½}$ remain constant.

Oral melatonin is absorbed by first-order kinetics, which has previously been demonstrated in doses up to 80 mg. The reported pharmacokinetic variables Cmax, Tmax, T1/2, AUC, Cl, Vd, and bioavailability of several studies are presented in Table below. A generally low bioavailability of oral melatonin has been documented in a number of studies, although displaying variable mean values ranging from 3 to 33 %. Three studies reported absolute bioavailability. Bioavailability ranged from 9 (dose 0.25 mg) to 33 % (dose 0.5 mg). Similarly, studies demonstrated a substantial intrastudy variation between subjects. The absolute bioavailability of oral melatonin tablets was studied in 12 normal healthy volunteers. Subjects were administered, in a randomized crossover fashion, melatonin 2 mg intravenously and 2 and 4 mg orally. Blood was sampled over approximately eight (estimated) half-lives. Both the 2 and the 4 mg oral dosages showed an absolute bioavailability of approximately 15%. Another study showed an oral bioavailability of 2.5% (Range: 1.7–4.7).

A single melatonin dose of 3 mg is expected to result in a maximum plasma concentration of about 3400 pg/mL, which is ≈ 60-times the peak nocturnal (endogenous) plasma melatonin Cmax, though both values are subject to considerable inter-individual variation.

It is generally agreed that the low bioavailability is caused by a considerable first-pass metabolism in the liver. A study addressed this issue by measuring the production of the main metabolite 6-hydroxymelatonin sulphate following oral and intravenous administration. Compared with intravenous injection, oral administration provided an increased metabolite/melatonin plasma level ratio, indicating liver metabolism as the main determinant of the low oral f. The significance of liver metabolism was also emphasized by other reports in which coadministration of cytochrome P450 (CYP) 1A2 enzyme drug substrates, such as fluvoxamine, caffeine, or oral contraceptives, along with exogenous melatonin, had a substantial impact on subsequent plasma melatonin levels. Finally, studies in liver cirrhosis patients also demonstrated reduced elimination rates and increased plasma melatonin levels.

Table 1: pharmacokinetic variables Cmax, Tmax, T1/2, AUC, Cl, Vd, and bioavailability of several studies

Melatonin dose/administration route/subgroup	C_{max} (pg/ml)	T_{max} (min)	$T_{1/2}$ (min)	AUC (pg/ml × min)	Cl; Cl/F (L/min)	V_D; V_D/F (L)	Bio (%)
2 mg/oral/gelatin-coated capsules	Fasting, 2800	Fasting, 15	32	222,720	–	–	–
	Fed, 6800	Fed, 30	–	482,160	–	–	–
2 mg/oral/slow-release pills	–	–	–	–	–	–	–
2 mg/oral/corn-oil preparation	Fasting, 3500	Fasting, 30	–	237,180	–	–	–
	Fed, 4400	Fed, 30	40	349,560	–	–	–
10 mg/oral	14,974	30	88	1.80×10^6	5.85	–	–
0.0005 mg/kg BW/IV/prepubertal	–	–	40	15,054	3.30	185	–
0.0005 mg/kg BW/IV/pubertal	–	–	47	18,006	2.70	173	–
0.0005 mg/kg BW/IV/adults	–	–	47	22,614	2.03	135	–
2 mg/oral	2175	52	61	237.77×10^3	–	–	14
4 mg/oral	5766	60	65	530.57×10^3	–	–	16
2 mg/IV	96,850	–	60	1.63×10^6	–	–	–
0.5 mg/oral	–	–	47	–	–	–	33[a]
0.25 mg/oral/male	244	23	36	14,160	–	–	9
0.25 mg/oral/female	624	23	45	42,084	–	–	17
0.023 mg (250 ml/h)/IV infusion/male	124.8	113.4	36	15,288	1.57	73.1	–
0.023 mg (250 ml/h)/IV infusion/female	169.0	110.4	41	21,846	1.09	53.8	–
0.4 mg/oral	405	78	108	95,700	6.32	1035	–

Melatonin dose/administration route/subgroup	C_{max} (pg/ml)	T_{max} (min)	$T_{1/2}$ (min)	AUC (pg/ml × min)	Cl; Cl/F (L/min)	V_D; V_D/F (L)	Bio (%)
4 mg/oral	3999	90	126	727.4×10^3	7.97	1602	–
6 mg/oral/+caffeine (smoker+non-smoker)	10,618	30	113			–	–
6 mg/oral/–caffeine (smoker+non-smoker)	4480	60	106	–	3.08	–	–
5 mg/oral/+fluvoxamine	25,100	–	804[b]	8.48×10^6	–	–	–
5 mg/oral/–fluvaxamine	2180	–	564[b]	372×10^3	–	–	–
6 mg/oral/wild-type genotype+OC	7900	60	36	684×10^3	12.50	–	–
6 mg/oral/wild-type genotype–OC	1800	60	37	138×10^3	132.50	–	–
6 mg/oral/variant genotype+OC	7200	60	38	654×10^3	15.63	–	–
6 mg/oral/variant genotype–OC	1700	45	49	144×10^3	94.00	–	–
5 mg/oral/immediate-release formulation (type A)	$A = 4823$	$A = 30$	$A = 38$	$A = 256,885$	–	–	–
10 mg/oral/pulsatile-controlled release formulation (type B/C)	$B = 3820$	$B = 45$	$B = 48$	$B = 507,911$	–	–	–
	$C = 4072$	$C = 210$	$C = 50$	$C = 595,400$	–	–	–
Dose not reported/IV	–	4	44	–	–	–	–
5 mg/oral/slow-release	8770	167	91	2.3×10^6	3.09	451	–
0.005 mg/IV bolus	–	–	28	5400	0.97	35	–
0.02 mg (10 ml/h)/IV infusion	72.1	–	45	–	0.97	63	–

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IV.3 Pharmacodynamics

Melatonin is the major hormone produced by the pineal gland. It is a lipid soluble substance with low molecular weight and is structurally related to serotonin and its precursor, the amino acid tryptophan. Melatonin plays a major role in the entrainment of the biological clock and in mediating the sleep wake cycle. The concentration of melatonin in blood is low during

daytime and high at night, due to light availability to inhibit the activity of an enzyme involved in the production of melatonin. The function of melatonin has been extensively investigated in animals and humans. Because of its possible role in influencing the circadian rhythm of sleep, melatonin has been used for treating sleep disorders including, jet-lag, shift work, delayed sleep phase syndrome, periodic sleep disorder in blindness and sleep and behavioural disorders in children with multiple brain damage.

Melatonin binds to melatonin receptor type 1A, which then acts on adenylate cyclase and the inhibition of a cAMP signal transduction pathway. Melatonin not only inhibits adenylate cyclase, but it also activates phospholipase C. This potentiates the release of arachidonate. By binding to melatonin receptors 1 and 2, the downstream signalling cascades have various effects in the body. The melatonin receptors are G protein-coupled receptors and are expressed in various tissues of the body. There are two subtypes of the receptor in humans, melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2). Melatonin binds to and activate both receptor types. When melatonin receptor agonists bind to and activate their receptors it causes numerous physiological processes. MT1 receptors are expressed in many regions of the central nervous system (CNS): suprachiasmatic nucleus of the hypothalamus (SNC), hippocampus, substantia nigra, cerebellum, central dopaminergic pathways, ventral tegmental area and nucleus accumbens. MT1 is also expressed in the retina, ovary, testis, mammary gland, coronary circulation and aorta, gallbladder, liver, kidney, skin and the immune system. MT2 receptors are expressed mainly in the CNS, also in the lung, cardiac, coronary and aortic tissue, myometrium and granulosa cells, immune cells, duodenum and adipocytes. The binding of melatonin-to-melatonin receptors activates a few signalling pathways. MT1 receptor activation inhibits the adenylyl cyclase, and its inhibition causes a rippling effect of non-activation; starting with decreasing formation of cyclic adenosine monophosphate (cAMP) and then progressing to less protein kinase A (PKA) activity, which in turn hinders the phosphorylation of cAMP responsive element-binding protein (CREB binding protein) into P-CREB. MT1 receptors also activate phospholipase C (PLC), affect ion channels and regulate ion flux inside the cell. The binding of melatonin to MT2 receptors inhibits adenylyl cyclase which decreases the formation of cAMP. As well it hinders guanylyl cyclase and therefore the forming of cyclic guanosine monophosphate (cGMP). Binding to MT2 receptors probably affects PLC which increases protein kinase C (PKC) activity. Activation of the receptor can lead to ion flux inside the cell.

Circadian Rhythm Sleep Disorders
There are several Circadian Rhythm Sleep Disorders (CRSD) where rhythm abnormalities are associated with lack of well-being and/or poor performance. These CRSD are shift work, jet lag, delayed and advanced sleep phase syndrome, irregular sleep-wake pattern and non-24-hour sleep-wake disorder. Suitably timed bright light is effective at hastening adaptation to phase shift. However, the use of bright light in some circumstances may be undesirable; in the case of the blind with neither conscious nor hypothalamic light perception, it is clearly inappropriate. The obvious solution to circadian desynchrony problems of this sort is a chronobiotic, a drug that shifts all circadian rhythms in the desired direction and acts as a zeitgeber to maintain stable phase once the latter is obtained. Presumably, exogenous melatonin can fulfil this role.

A study on melatonin administered in a physiological dose intravenously for 3 hours showed a remarkable similarity to the original melatonin profile, particularly given the differences in dosing regimens and the difficulties encountered when trying to discern the endogenous melatonin profile from exogenous melatonin levels. Another interesting result of this study

was that at least one dose regimen affected the area under the curve (AUC) of the post-treatment endogenous melatonin profile.

When suitably timed most studies indicate that fast release preparations are able to hasten adaptation to phase shift. Sustained release formulations, or multiple dosing regimens, may optimise phase shifting while minimising the total dose. These may be particularly useful when minimising direct soporific 'side effect' of melatonin that appears to be related to the maximum concentration.

In a similar vein a conducted study suggested, that for several indications it seems reasonable to develop delivery systems that can maintain high melatonin levels throughout the sleep episode or even preferentially deliver melatonin in the second half of the sleep episode. And which way of administration mimicked endogenous melatonin release most physiologically. In 12 healthy young male volunteers an oral controlled-release capsule, an oral transmucosal form and a transdermal patch were tested. The melatonin concentrations reached by the transdermal patch and the controlled release capsule differed much between the various subjects. The oral transmucosal form was able to mimic the physiological plasma profiles of both melatonin and its metabolite, 6-sulfatoxymelatonin in all subjects.

Light plays a dual role: first, as a zeitgeber for the biological clock, i.e. as a synchronising and phase shifting agent, and second, it has acute (direct) physiological effects that increase alertness. Melatonin also plays a dual role. First, it has established zeitgeber properties, with phase advances in the afternoon and evening before endogenous melatonin onset, and phase delays in the second half of the night through the morning. This phase response curve (Figure 1) is roughly opposite to that of light, which induces delays in the evening after melatonin onset and advances in the latter hours of sleep and early morning.

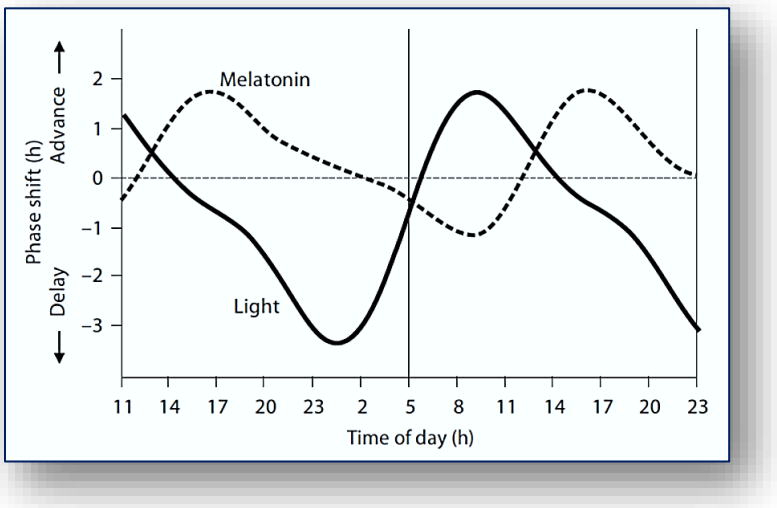

Figure 1. Schematic representation of shifts (in hours) in the circadian system according to time of day (or circadian phase) of administration. Light (full line) given in the early morning (after the core body temperature minimum at approximately 5 a.m.) shifts the clock earlier (phase advance), in the evening (before the core body temperature minimum) to later (phase delay). Melatonin (broken line) has nearly opposite effects: morning melatonin induces a phase delay, and evening melatonin a phase advance

Secondly, exogenous melatonin has acute (direct) effects that increase sleepiness and promote sleep onset (even including daytime napping in controlled experiments). Since

evening melatonin administration induces a phase advance and morning melatonin a phase delay, with careful timing it can guide the circadian phase of increased sleep propensity toward the desired bedtime. Melatonin can induce sleep when the homeostatic drive to sleep is insufficient, and it can also inhibit the drive for wakefulness that emanates from the circadian pacemaker. That is why exogenous melatonin can act as soporific agent, a chronobiotic, or both.

Effects of exogenous melatonin on core body temperature
Under the entrained conditions of normal daily life, major nocturnal sleep is typically initiated 5-6 hours before the temperature minimum and is terminated shortly after the minimum. A study showed that the process of sleep initiation is most likely to occur when body temperature is declining at its maximum rate, and it is most successfully accomplished at this phase of the temperature cycle. To clarify whether the melatonin rise and the core body temperature decline are not only temporally but also causally related, manipulations of nocturnal melatonin levels have been used. Both complete suppression of nocturnal melatonin levels by administration of the β-blocker atenolol and increase of melatonin to pharmacological values by its exogenous administration at night do not immediately modify the phase of the core body temperature nadir.

In one study administration of doses below 1 mg (0.3 or 0.1 mg) melatonin, which are claimed to reproduce physiological plasma levels of melatonin, failed to reduce core body temperature. On the basis of this finding, it could be suggested that only levels of melatonin in the pharmacological range, but not in the physiological range, exert an effect on core body temperature. However, reproduction of physiological levels of melatonin in blood may be useful to study the peripheral versus the central effects of the hormone.

Indeed, pharmacokinetic studies including primates have suggested that within the ventricular cerebrospinal fluid, levels of melatonin similar to those observed during the endogenous production of the hormone, may be obtained only by increasing its peripheral levels to the pharmacological range. Cerebrospinal fluid is believed to represent the preferential route for melatonin to reach the hypothalamus. Therefore, administration of low melatonin doses that maintain physiological levels of the hormone in peripheral plasma for a limited period of time, actually might be insufficient and inadequate to induce its possible central action on thermoregulation.

It is reasonable to assume that following the administration of melatonin, a certain time is required for the body to reduce its heat content. Indeed, the maximal effect on core body temperature reduction becomes fully manifested at approximately 4 h after oral administration of pharmacological doses (2.5 mg) of the hormone. At this time, the values of core body temperature are about 0.3 degrees Celsius lower with melatonin than those following the administration of placebo, and this difference is maintained for the entire period throughout which plasma melatonin levels remain elevated.

Neurotransmitters can modify core body temperature regulation. Among these, serotonin is believed to decrease and prostaglandins to increase core body temperature. Experimental evidence obtained in animals indicates that in the brain, administration of melatonin increases serotonin levels and serotonergic neurotransmission and is a potent inhibitor of prostaglandin synthesis. This will result in lowering of the body temperature.

<u>Effects of exogenous melatonin on circadian rhythms</u>

Phase shift of the endogenous melatonin rhythm by exogenous melatonin

A study found a relationship between the time of melatonin administration relative to the pre-treatment rise of endogenous melatonin and the resulting phase advance of the melatonin rhythm. This PRC is nearly the opposite in phase with the PRCs for light exposure: melatonin delays circadian rhythms when administered in the morning and advances them when administered in the afternoon or early evening.

Figure 2 illustrates the relationship between the timing of exogenous melatonin administration and the measured phase shifts of the endogenous melatonin rhythm.

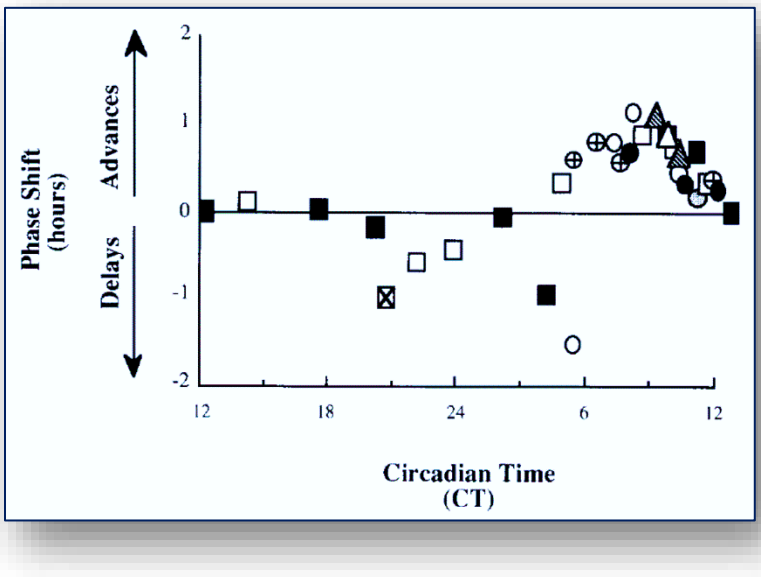

Figure 2. Phase shifts of the dim light melatonin onset (DLMO) as a function of circadian time (CT) for all subjects' 30 trials, providing the first evidence for a human melatonin phase-response curve (PRC). Each of the nine subjects has a separate symbol.

Published data described a log-linear relationship between the dose of melatonin and the magnitude of phase shifts in the DLMO for doses of 0.05 mg, 0.5 mg and 5 mg. Melatonin treatment also induced acute, dose-dependent temperature suppression and decrements in alertness and performance efficiency. Earlier sleep onset, offset and better sleep quality were associated with increasing doses of melatonin. The day after melatonin administration in the afternoon, a significant dose-dependent phase advance in the plasma melatonin onset time and temperature nadir was observed with a trend for the alertness rhythm to phase advance. Study concerned that some of the reported 'phase shifts' in the melatonin profile may reflect a change in the shape of the endogenous melatonin profile due to endocrine feedback effects from the melatonin administration. The onset of the endogenous melatonin curve could be advanced by about 1.55 hour, while no significant phase advance was observed for offset of the melatonin curve. Similar changes of the shape of the curve have been found before and have led to the hypothesis of the two-oscillator model with an oscillator for the onset (“evening” oscillator) and for the offset of melatonin (“morning” oscillator). Published additional experimental evidence that supports the hypothesis that evening onset and morning offset of the human melatonin secretion are regulated by separate circadian processes. The study also provide evidence that suggests that these processes exhibit opposite phase responses to the administration of melatonin. The study found that morning treatment with melatonin counteracted the phase-advancing effect of morning light on the offset of secretion but potentiated its phase advancing effect on onset of secretion. Thus, when morning light treatments and morning melatonin treatments were combined, the intrinsic duration of

melatonin secretion increased.

Effects on Delayed Sleep Phase Syndrome (DSPS)
DSPS or Delayed Sleep-Wake Phase Disorder is defined as a disorder in which the major sleep episode is delayed in relation to the desired clock time and therefore results in symptoms of sleep-onset insomnia or difficulty in awakening at the desired time. Individuals suffering from DSPS, despite having completely normal sleep architecture and sleep duration, experience great difficulty falling asleep before 12 am, if not later, as well as rise at acceptable hours of the morning. DSPS is probably the most common of the intrinsic circadian sleep disorders, or at least the most commonly diagnosed. Based on an early survey, it was estimated that approximately 7% of people diagnosed with disorders of initiating and maintaining sleep meet criteria for DSPS.

Two methods to treat DSPS are known in literature: chronotherapy and administration of melatonin. Chronotherapy is a drug-free rescheduling treatment, designed to resynchronise sleep with the patient's biological clock. Since patients with DSPS have inadequate capacity to achieve phase advance shifts of the circadian pacemaker, a phase delay route must be chosen.

The first study on the effects of melatonin on DSPS described the actions of melatonin on the sleep-wake cycle were investigated by means of a randomised double-blind placebo-controlled trial in 8 subjects with DSPS. The study concluded that melatonin may act as a phase-setter for sleep-wake cycles in subjects with a DSPS, with no influence on the alertness.

A further study describes routine treatment of the administration of melatonin 5mg administered at 22:00h for 6 weeks to 61 subjects diagnosed with DSPS. The efficiency of the melatonin treatment and its possible side effects were investigated by means of a survey questionnaire. Over 95% of the subjects reported melatonin to reduce the complaints with almost no side effects. However, more than 90% reported a relapse to their pre-treatment sleeping patterns within 1 year of the end of treatment. In more than a quarter of them the relapse occurred within 1 week. The time of administration of the medication was individualised on basis of plasma curves of endogenous melatonin. Conducted study had shown that advancement of the endogenous melatonin curve by exogenous melatonin was largest at CT 9, as illustrated by figure 4. Since CT 14 is the DLMO we administered melatonin 5 hours before the individual DLMO. The number and seriousness of the complaints were decreased and an advance of the rising slope of the melatonin curve was found.

Effects on shift work disorder
There is a report of insomnia and/or excessive sleepiness, accompanied by a reduction of total sleep time, which is associated with a recurring work schedule that overlaps the usual time for sleep.
Complaints during the period of night work, such as the poor quality of day sleep, may be reduced by increasing the rate of adaptation of the circadian rhythm to the shifted sleep period. Bright light administration during the early part of the night appears to be effective in facilitating the delay of the temperature rhythm and thus can help to re-establish the association between the temperature trough and the sleep period. In a similar way, melatonin administration in the morning may facilitate a phase delay.

Only a few field studies concerning night work have been published. Several night workers phase shift themselves, without treatment. Because of the variability in phase shifting, it may be necessary to focus on subjects who do not shift, or only partially shift to observe a response to melatonin administration. In a placebo-controlled laboratory study where shift work situation was simulated and compared adaptation to night shift in three groups of subjects. The first treatment group received timed exposure to bright light, the second treatment group received 2 mg of exogenous melatonin, and the placebo group received either dim red light at less than 50 lux or a placebo capsule. Using the DLMO as a circadian marker, the bright-light group had the largest shift (an average delay of 8.8 h), whereas there was no significant difference in phase shift between the placebo and the melatonin groups (a delay of 4.2 h and 4.7 h respectively). The failure of melatonin treatment to induce greater phase shifts than placebo might be related to the divided dose regimen (4 mg in three divided doses across the day sleep period) that fell on both the advance and delay portion of the melatonin response curve.

A study found that the timing of melatonin production was distinctly different in a group of nine permanent night-workers compared to a group of day-active controls. This indicates a major adaptation of the circadian pacemaker to the atypical schedule for activity, sleep and light exposure. However, there is a suggestion that adaptation remains incomplete (and perhaps unstable) because the timing of sleep appears to be at an earlier circadian phase than is typical for day active subjects. Until now, no studies have been done that conform the existence of a (relative) desynchronization by longitudinal measurements of melatonin phase together with precise measurements of sleep.

The authors of a randomised placebo-controlled double-blind cross-over study in 24 subjects, with objective sleep data and with a rotating schedule. The subjects had taken melatonin 0.55 mg or placebo for two weeks; found an impressive variability in the magnitude and direction of phase shifting. Also, other authors found variable responses in sleep shifting effects under consistent work schedules.

Jet lag

Several studies have also shown that exogenously administered melatonin can alleviate jet lag symptoms both by causing sleep propensity and by regulating timing of the sleep wake-cycle.

It was noted that transmeridian travel affects the sleep, circadian rhythms, and daytime activity of travellers, effects which often take several days to resynchronize to local environmental conditions. The time required for adaptation is generally determined by the size of the phase shift and Zeitgeber strength. This approximates to an adaptive shift of 1-1.5 h per day, with eastbound flight causing a greater prolongation of symptoms when compared to westbound flights. A study has shown that melatonin administration has been shown to shift circadian rhythms in humans. This effect is a key factor in melatonin's actions in reducing jet lag symptoms, the therapeutic value of which has now been demonstrated in numerous studies.

Hypnotic effects of exogenous melatonin

A review the numerous published studies on the acute effects of melatonin on human sleepiness and sleep, indicated that except a few negative or inconclusive results, the majority of these studies have shown that a substantial increase of circulating melatonin levels was associated with sedation, fatigue, decreased alertness, significantly increased reaction time,

shortening of latency to sleep, increased sleep efficiency and total sleep time, or increased sleep propensity. A hypnotic effect by exogenous melatonin in humans was established with oral doses of 1-6 mg to 100 mg. When melatonin doses under 1 mg were tested, the dose dependency was revealed. All the doses tested augmented subjective sleepiness or shortened latency to sleep onset. A study compared the effects of 0.33 mg and 1 mg melatonin and confirmed that increasing circulating melatonin levels to within the physiological range promotes polysomnographically detected sleep onset of afternoon naps and of overnight sleep in young healthy volunteers. This effect of melatonin treatment occurs independently of the time of administration. Since melatonin induced shifts in circadian rhythmicity are limited to 20-60 min per day after administration of a single dose of the hormone at a favourable time point the observation of time independence is a strong argument against interpreting the acute sleep-promoting effect of melatonin as a part of its phase shifting activity. On the other hand, other view that there is not yet convincing body of evidence that melatonin improves sleep in insomniacs with noncircadian sleep disturbances. So, in this view the sleep promoting effects are strongly connected to the circadian effects.

All studies that have investigated daytime administrations of melatonin reported increased sleepiness even at doses that do not increase plasma levels of melatonin beyond its physiological level. By contrast, night-time increase in sleepiness was achieved only after administration of high doses. Based on these findings and on the precise coupling between the endogenous nocturnal increase in melatonin secretion and the opening of “the sleep gate”, an abrupt transition from a period of low sleep propensity to a period of high sleep propensity that persists during the night period, this study suggested that melatonin participates in the regulation of the sleep-wake cycle by inhibiting the central nervous system wakefulness generating system. Clinical findings on decreased levels of nocturnal melatonin in chronic insomniacs and on the efficacy of exogenous melatonin in improving sleep in melatonin deficient insomniacs, are congruent with this hypothesis.

The consensus is that the circadian drive for sleep is lowest as the circadian temperature reaches its crest. Constant routine studies carried out immediately on release from entrainment have demonstrated that in young subjects the body temperature crest is located in the evening between 17-19hr. After this nadir in sleep propensity there is a sudden and rapid increase in the ability to fall asleep. This has been referred to as the opening of the sleep gate or the dissipation of the circadian drive for wakefulness. In some protocols, an increase in the ability to fall asleep has also been observed approximately 10 to 14 h after the temperature minimum. However, the magnitude of the mid-afternoon increase in the ability to fall asleep is much smaller than the nocturnal increase in sleep propensity.

Melatonin exerts some effects on the main characteristics of human sleep, that is a shorter latency to sleep onset, better sleep consolidation and tendencies of decrease in the duration of stage 4 sleep and increase in the duration of stage 2 sleep. Some studies suggest that higher doses of melatonin can increase REM sleep.

Two studies pointed out that the effects of melatonin are, to some extent similar to the changes induced by benzodiazepine hypnotics. This may lead to the suggestion that melatonin's hypnotic effects are exerted through the same mechanism. Reports that melatonin modifies GABA-ergic neural transmission also support this assertion. Interestingly the effects of melatonin on EEG spectra could not be blocked by flumazenil, which may indicate that the effects are not mediated by GABAa benzodiazepine receptor complex or that a unique subtype of the GABAa - benzodiazepine receptor complex is involved in mediating

melatonin effects.

IV.4 Clinical efficacy

Eleven clinical trials are described that investigated the effectiveness and safety of melatonin in the treatment of jet lag and were published between 1987 – 2004, reflecting the longstanding scientific interest in the potential use of melatonin to alleviate symptoms of jet lag. All the clinical trials investigating jet lag were either placebo controlled or included an active comparator. More recent clinical trials have also been conducted, as well as a number of systematic reviews of melatonin in sleep disturbance, including jet lag; these include a Cochrane review (2022) of ten clinical trials that specifically investigated the effect of melatonin treatment of jet lag. Melatonin at doses of between 0.5 mg and 8 mg against either a placebo or a short acting hypnotic were included. A dose of 5 mg was more effective than 0.5 mg but there was no gain from doses higher than 5 mg. The conclusion from the review was that melatonin in short term use is safe and effective in reducing the symptoms of jet lag. Two additional systematic reviews that investigated use of melatonin in jet lag also concluded a clinically relevant effect. The published evidence points to sustained release formulations of melatonin being less effective than immediate release formulations for the treatment of jet lag; however, sustained release formulations may be advantageous in other types of sleep disturbance. Provided the dose recommendations for the proposed product are adhered to, in respect of timing and the maximum recommended dose of 6 mg for up to a maximum of 5 days, the safety profile is favourable. Drowsiness and reduced alertness are the main risks. Warnings are in place in the product information in regard to driving and operating machinery.

Randomised controlled trials in jet lag

A study evaluated seventeen healthy volunteers (10 women and 7 men, aged 29-68) that were flown from London to San Francisco between that remained there for 14 days prior to flight home. Subjects took melatonin (N = 8, 5 women, 3 men) or placebo in a double-blind design, at 18.00h local time for three days before the return flight and at bedtime (22.00-24.00h) in Great Britain for four days. For three days before departure and on days 1-7, 14, 15, 21 and 22 after their return subjects collected 6-hourly sequential urine samples and kept a daily sleep log. They recorded mood and oral temperature 2 hourly and performed logical reasoning and letter cancellation tests 4 hourly from 08.00h (or wake up time) to 24.00h (or bedtime) whichever was the earlier. Urine was also collected for 48 h prior to departure from the U.S.A. On day 7 after their return subjects rated ‘jet lag’ (10 cm visual analogue scale—VAS) from 0 (insignificant) to 100 (very bad).

Melatonin significantly improved ‘jet lag’ ($p= 0.009$). Comparisons by ANOVA between jet-lagged placebo subjects (N = 7) and melatonin (N = 8) showed decreased sleep latency with melatonin ($p= 0.0397$) which correlated positively with jet lag ratings, $p< 0.001$. Sleep quality was significantly improved in the melatonin group and correlated negatively with jet-lag ratings ($p<0.001$). No important differences were found in temperature, or performance data. Baseline differences were present in some performance ratings but no other variables. Melatonin treated subjects tended to be more alert than placebo subjects, especially at bedtime. They were also less depressed. Endogenous melatonin and Cortisol rhythms resynchronized more rapidly in melatonin subjects ($p= 0.0216$ and $p= 0.0299$ respectively, absolute acrophase shifts). Cortisol rhythms indicated adaptation to U.S.A. time in 14 days.

These data suggest that melatonin can alleviate jet-lag after Eastward flight over eight time zones. Presumably its affects are primarily on sleep latency, quality, and directly or indirectly on some hormonal rhythms.

A further study used a double-blind cross-over design in 52 of 61 participants flying from the UK to Australia & New Zealand and back completed the crossover. Subjects took melatonin 5mg or placebo. For eastward flights this was taken for 2 days before the flight at the local time, which corresponded to 2am at the destination time zone, and for 4 days after arrival at the local bedtime [’pre+post’]. For westward flights melatonin or placebo was taken at the local bedtime for 4 days after arrival.

A double blind, placebo-controlled crossover trial investigated the effect of melatonin on jet lag after flights from Auckland to London and back in twenty volunteers with experience of transcontinental flights (eight women and 12 men aged 28 to 68). The study was designed so that feelings of jet lag and mood could be closely monitored over the 10 days after the flight, thus allowing closer examination of the readjustment. They received melatonin (or placebo) 5 mg three days before flight, during flight, and once a day for three days after arrival. As end-point, the symptoms of jet lag were used; visual analogue scale for feelings of jet lag and tiredness; profile of moods states questionnaire for vigour-activity and fatigue-inertia; and retrospective ratings 10 days after arrival of sleep pattern, energy, and daytime tiredness.

Feelings of jet lag were less for subjects taking melatonin (mean score 2.15 vs 3.4); these subjects took fewer days than the placebo group to establish a normal sleep pattern (2.85 vs 4.15), to not feel tired during the day (3.0 vs 4.6), and to reach normal energy levels (3.25 vs 4.7). Results for fatigue-inertia and vigour-activity were similar. For all subjects jet lag was more severe on the return (westward) than the outward (eastward) journey.

A further study on thirty-seven healthy volunteers accustomed to intercontinental flights who usually experienced subsequent discomfort after an eastward journey were included in a protocol designed to evaluate the alleviation of jet-lag syndrome by melatonin.

Subjects took an 8 mg melatonin or a placebo capsule, first on the day of the nocturnal return flight (day 1 of the study) at 22-n hr, 22 hr (i.e., 10 PM) being the usual time of the melatonin secretion onset and n the time-lag between the American departure point and France, then for 3 consecutive days in France at bedtime, around 10 PM-11 PM (days 2, 3, 4 of the study). In addition, melatonin and placebo courses were randomly administered once in 3 people repeatedly traveling between America and France, with an interval of more than 6 months between the two studies.

Thirty self-rating questionnaires, 15 in each group, were correctly filled in (15 subjects under melatonin, 8 men, 7 women; 15 subjects under placebo, 10 men, 5 women). Ten subjects (5 in each group) dropped out of the study, none of them because of side effects. The three subjects involved in a crossover trial fully complied with the protocol. On day 8, self-ratings significantly discriminated between melatonin and placebo for global treatment efficacy ($p < 0.05$ when comparing the medians of efficiency scores, 73 versus 48 for the melatonin and the placebo groups, respectively). For the three subjects receiving randomly melatonin and placebo during two different courses, all the scores were in favor of melatonin treatment. Compared with placebo, melatonin demonstrates an overall efficiency in alleviating jetlag in subjects chosen for having already experienced significant discomfort after an eastward flight, therefore included in the trial according to a strict criterion.

The efficacy of oral melatonin in alleviating jet lag in flight crew after a series of international flights was also investigated. The optimal time for taking melatonin in this group was also investigated. In a double-blind placebo-controlled trial, 52 international cabin crew were randomly assigned to three groups; early melatonin (5 mg started 3 days prior to arrival until 5 days after return home); late melatonin (placebo for 3 days then 5 mg melatonin for 5 days); and placebo. Daily ratings showed a trend in jet lag, mood, and sleepiness measures toward an improved recovery in the late melatonin group and a worse recovery in the early melatonin group as compared to placebo. Retrospective ratings made 6 days after arrival showed the late melatonin group reported significantly less jet lag and sleep disturbance following the flight compared to placebo. The late melatonin group also showed a significantly faster recovery of energy and alertness than the early melatonin group, which reported a worse overall recovery than placebo. These findings show melatonin may have potential benefits for international aircrew.

A double-blind, randomized, placebo-controlled study was conducted to compare the impact of various dosage forms of melatonin and placebo on jet lag symptoms in 320 volunteers who had flights over 6 to 8 time zones. The volunteers received either melatonin 0.5-mg fast-release (FR) formulation, melatonin 5-mg FR formulation, melatonin 2-mg controlled-release (CR) formulation, or placebo. The study medication was taken once daily at bedtime during 4 days after an eastward flight. The volunteers completed the Profile of Mood States (POMS), sleep log, and symptoms questionnaires once daily and the Karolinska Sleepiness Scale (KSS) three times daily prior to departure and during the 4 days of medication intake postflight.

A total of 234 (73.1%) participants were compliant and completed the study. The FR melatonin formulations were more effective than the slow-release formulation. The 5-mg FR formulation significantly improved the self-rated sleep quality ($p < .05$), shortened sleep latency ($p < .05$), and reduced fatigue and daytime sleepiness ($p < .05$) after intercontinental flight. The lower physiological dose of 0.5 mg was almost as effective as the pharmacological dose of 5.0 mg. Only the hypnotic properties of melatonin, sleep quality and sleep latency, were significantly greater with the 5.0-mg dose.

A randomized, double-blind trial of placebo and three alternative regimens of melatonin (5.0 mg at bedtime, 0.5 mg at bedtime, and 0.5 mg taken on a shifting schedule) for jet lag was conducted with the aim of to validate a new rating scale for measuring severity of jet lag and to compare the efficacy of contrasting melatonin regimens to alleviate jet lag. The subjects were 257 Norwegian physicians who had visited New York for 5 days. Jet lag ratings were made on the day of travel from New York back to Oslo (6 hours eastward) and for the next 6 days in Norway. The main outcome measures were scale and item scores from a new, syndrome-specific instrument, the Columbia Jet Lag Scale, that identifies prominent daytime symptoms of jet lag distress.

There was a marked increase in total jet lag score in all four treatment groups on the first day at home, followed by progressive improvement over the next 5 days. However, there were no significant group differences or group-by-time interactions. In addition, there was no group effect for sleep onset, time of awakening, hours slept, or hours napping. Ratings on a summary jet lag item were highly correlated with total jet lag scores (from a low of $r = 0.54$ on the day of travel to a high of $r = 0.80$ on day 3). The internal consistency of the total jet lag score was high on each day of the study.

A study was conducted to examine the effects of oral melatonin in alleviating jet-lag by investigating its effects on subjects who had flown from London to Eastern Australia, 10 time-zones to the east. Melatonin (5 mg/day or placebo capsules were administered to 14 experimental (13 males and 1 female) and 17 control subjects (15 males and 2 females), respectively, in a double-blind study; the time of administration was in accord with the current consensus for maximizing its hypnotic effect. Grip strength and intra-aural temperature were measured on alternate days after arrival at the destination, at four different times of day (between the times 07:00 - 08:00 h, 12:00 - 13:00 h, 16:00 - 17:00 h and 19:00 - 20:00 h local time). In addition, for the first 6 - 7 days after arrival in Australia, subjective ratings of jet-lag on a 0 - 10 visual analogue scale and responses to a Jet-lag Questionnaire (incorporating items for tiredness. sleep, meal satisfaction and ability to concentrate) were recorded at the above times and also on retiring (at about midnight). Subjects continued normally with their work schedules between the data collection times.

Subjects with complete data (13 melatonin and 13 placebo subjects), in comparison with published data, showed partial adjustment of the diurnal rhythm in intra-aural temperature after 6 days. A time-of-day effect was evident in both right and left grip strength during adjustment to Australian time; there was no difference between the group taking melatonin and that using the placebo. Right and left grip strength profiles on day 6 were adjusted either by advancing or delaying the profiles, independent of whether subjects were taking melatonin or placebo tablets. Subjects reported disturbances with most measures in the Jet-lag Questionnaire but, whereas poorer concentration and some negative effects upon sleep had disappeared after 3 - 5 days, ratings of jet-lag and tiredness had not returned to 'zero' (or normal values), respectively, by the sixth day of the study. Subjects taking melatonin showed no significant differences from the placebo group in perceived irritability, concentration, meal satisfaction, ease in getting to sleep and staying asleep, frequency of bowel motion and consistency of the faeces. These results suggest that, in subjects who, after arrival, followed a busy schedule which resulted in frequent and erratic exposure to daylight, melatonin had no benefit in alleviating jet-lag or the components of jet-lag, and it did not influence the process of phase adjustment.

A further study was conducted that compared the effectiveness and tolerability of a chronobiotic (melatonin) with a hypnotic (zolpidem) and the combination of both substances to alleviate jet lag symptoms associated with eastward travel. This double-blind, randomized, placebo-controlled study is based on 137 volunteers flying from Switzerland to the American continent and back (6-9 time zones). The participants either received melatonin 5 mg (n = 35), zolpidem 10 mg (n = 34), a combination thereof (n = 29) or placebo (n = 39) on the eastbound flight back to Switzerland and once daily at bedtime on 4 consecutive days after the flight. The test battery included daily sleep logs, symptoms questionnaires, and the Profile of Mood States (POMS). Also, on the last treatment day, Visual Analogue Scales (VAS) were completed to assess overall jet lag ratings and treatment effectiveness. Baseline data were collected on 4 consecutive days 2 wk after the flight. During post-flight treatment and baseline, motor activity was assessed in a subgroup of 49 subjects using wrist-worn ambulatory monitors.

The self-rated sleep quality was significantly improved by zolpidem, especially during the night flight. Subjects taking zolpidem reported significantly less jet lag and zolpidem was rated as the most effective jet lag medication. However, zolpidem and the combination melatonin/zolpidem were less well tolerated than melatonin alone; adverse event reports

included nausea, vomiting, amnesia and somnambulia to the point of incapacitation. Confusion, morning sleepiness and nausea were highest in the combination group. All active treatments led to a decrease of jet lag severity with zolpidem being the most effective treatment, particularly in facilitating sleep on night flights. Potential individual adverse reactions to this hypnotic must be considered.

Systematic reviews
A systematic review was conducted to assess the effectiveness of oral melatonin taken in different dosage regimens for alleviating jet lag after air travel across several time zones. The selection criteria were randomised trials in airline passengers, airline staff or military personnel given oral melatonin, compared with placebo or other medication. Outcome measures consisted of subjective rating of jet lag or related components, such as subjective wellbeing, daytime tiredness, onset and quality of sleep, psychological functioning, duration of return to normal, or indicators of circadian rhythms. Ten trials met the inclusion criteria. All compared melatonin with placebo; one in addition compared it with a hypnotic, zolpidem. Nine of the trials were of adequate quality to contribute to the assessment, one had a design fault and could not be used in the assessment.

Eight of the ten 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 are similarly effective, except that people fall asleep faster and sleep better after 5mg than 0.5mg. Doses above 5mg appear to be no more effective. The relative ineffectiveness of 2 mg slow-release melatonin suggests that a short-lived higher peak concentration of melatonin works better. The estimated number needed to treat (NNT) is 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 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 incidence of other side effects is low. Case reports suggest that people with epilepsy, and patients taking warfarin may come to harm from melatonin.

This review concluded that melatonin is remarkably effective in preventing or reducing jet lag, and occasional short-term use appears to be safe. It should be recommended 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. Travellers crossing 2-4 time zones can also use it if need be.

Another review looked at the use of melatonin for the treatment of a number of categories of sleep disorders, including primary sleep disorders, secondary sleep disorders, and sleep restriction, in a number of different populations. Moreover, the review looked not only at the safety and effectiveness of melatonin for the treatment of sleep disorders, but also the pharmacology of exogenous melatonin and the physiology of endogenous melatonin, to provide a comprehensive overview of the state of research in this area.

Two previous systematic reviews examining the use of melatonin for the alleviation of jet lag concluded that melatonin is effective in alleviating the symptoms of jet lag. The results of the current review suggest that melatonin does not affect either sleep onset latency or sleep efficiency in jet lag sufferers or people suffering from shift-work disorder. Taken together, the findings of the current review and those of previous reviews suggest that the effectiveness

of melatonin in alleviating jet lag may not involve alleviation of the sleep disturbance, but rather, the daytime fatigue associated with jet lag.
In relation to safety of melatonin, the findings of this review suggest that exogenous melatonin is a relatively safe substance when used in the short term, over a period of days or weeks, and is safe at relatively high doses and in various formulations.
However, the safety of exogenous melatonin when used in the long-term, over months and years, remains unclear.

Another systematic review with meta-analysis was used to determinate the efficacy and safety of exogenous melatonin in managing secondary sleep disorders and sleep disorders accompanying sleep restriction, such as jet lag and shift work disorder. The efficacy review included randomised controlled trials; the safety review included randomised and non-randomised controlled trials.

Six randomised controlled trials with 97 participants showed no evidence that melatonin had an effect on sleep onset latency in people with secondary sleep disorders (weighted mean difference -13.2 (95% confidence interval -27.3 to 0.9) min). Nine randomised controlled trials with 427 participants showed no evidence that melatonin had an effect on sleep onset latency in people who had sleep disorders accompanying sleep restriction (-1.0 (-2.3 to 0.3) min). 17 randomised controlled trials with 651 participants showed no evidence of adverse effects of melatonin with short term use (three months or less).

A systematic review was conducted using Samueli Institute's Rapid Evidence Assessment of the Literature (REAL©) process to determine the evidence base for melatonin as an agent to optimize sleep or improve sleep quality, and generalize the results to a military, civilian, or other healthy, active, adult population. Multiple databases were searched yielding 35 randomized controlled trials (RCTs) meeting the review's inclusion criteria, which were assessed for methodological quality as well as for melatonin effectiveness. The majority of included studies were high quality (83.0%). Overall, according to Grading Recommendations, Assessment Development and Evaluation (GRADE) methodology, weak recommendations were made for preventing phase shifts from jet lag, for improving insomnia in both healthy volunteers and individuals with a history of insomnia, and for initiating sleep and/or improving sleep efficacy. Based on the literature to date, no recommendations for use in shift workers or to improve hormonal phase shift changes in healthy people can be made at this time. Larger and longer-duration RCTs utilising well characterised products are needed to warrant melatonin recommendations in young, healthy adults.

Another review used the Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information, they generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making. The information on the use of melatonin is based on 11 randomized studies. Ten studies reported global jet lag symptoms. However, only four studies provided data in a way that could be added to a meta-analysis. Generally, all studies reported side effects, but only three did so systematically. Melatonin probably reduces the global symptoms associated to jet lag syndrome in travellers crossing more than five time zones. The certainty of the evidence is moderate. It is not clear whether the use of oral melatonin is associated to adverse effects (nausea, tiredness, drowsiness and headaches) because the certainty of the evidence is very

low. However, no serious adverse effects were reported in any of the participants across the studies.

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.
Melatonin has been extensively studied in humans and animals for nearly 30 years.
Only mild adverse effects, such as dizziness, headache, nausea and sleepiness have been reported. No studies have indicated that exogenous melatonin should induce any serious adverse effects. Similarly, randomized clinical studies indicate that long-term melatonin treatment causes only mild adverse effects comparable to placebo.

A study showed that short-term melatonin is a relatively safe substance consistent with OTC usage. Long-term usage indicators from spontaneous reporting, studies of 6 months to 1 year, lack of US reports despite ready availability there for over 15 years, and long-term use of medicines that increase endogenous melatonin levels substantially, give no cause for concern.
The most common adverse events for melatonin 2 mg prolonged-release tablet (CIRCADIN) in clinical trials were: headache, nasopharyngitis, back pain and arthralgia.
These were rated common (i.e. 1%-10% of users) in both the CIRCADIN and placebo treated groups. Adverse events caused discontinuation in 2.9% of the CIRCADIN patients across the studies versus 4.0% of the placebo recipients. The safety profile during 3 weeks and 26 week treatment periods in studies was comparable to placebo with no withdrawal and rebound effects. No tolerance, rebound, or withdrawal effects were reported in an open study of 12 months treatment with CIRCADIN in 96 patients. Overall adverse experience for adverse events occurring with a frequency ≥ 1%.

Adverse reactions of melatonin in patients with jet lag
Nine randomised control trial reports note symptoms, but only the studies by two trials looked for symptoms systematically. The first found no statistically significant differences in the incidence of symptoms between melatonin and placebo. Some symptoms - daytime sleepiness, dizziness, headache and loss of appetite - were most frequent on day 1 after the flight and became less frequent on the next 3 days of treatment; these were probably symptoms of jet-lag. The zolpidem+melatonin group felt significantly sleepier in the morning, while the melatonin group felt least sleepy. The combination group also felt significantly more confused and more nauseated than all other treatment groups. Ear/ nose/ throat problems were most frequent in melatonin users; pruritus was least frequent in this group. The second trial asked participants to list any minor medical problems, and one was more frequent after melatonin (p= 0.036): a disorientating 'rocking' feeling as though they were on a boat.

Most adverse events or symptoms in the other six studies can be regarded as no more than qualitative pointers. However, hypnotic effects after melatonin occurred in 5 of the studies, affecting about 10% of the participants. Others included headache or 'heavy head', disorientation, nausea, and gastrointestinal problems. One individual experienced difficulty in swallowing and breathing within 20 minutes of taking the first dose of 0.5mg melatonin, symptoms which subsided after 45 minutes. This person stopped taking the capsules, but agreed to take another single dose on another occasion to see if the symptoms would recur. They did, but were somewhat milder. All the adverse events reported in the trials occurred during treatment and appear to have been short-lived.

Adverse effects in humans reported in the literature

General symptoms
These different adverse effects have been reported in the scientific literature, mainly during clinical trials to assess the efficacy and safety of melatonin.

Headache
Two meta-analyses of the clinical data on the efficacy and safety of melatonin administered for primary and secondary 26 sleep disorders. For the meta- analysis relating to primary sleep disorders, 10 studies involving approximately 222 participants were selected for the safety analysis. The doses of melatonin implicated in these studies were not specified. For the meta-analysis on the secondary disorders, seven studies were selected, involving 164 participants. The doses of melatonin administered were between 0.5 and 10 mg. The adverse effects most often described were headaches, dizziness and nausea, but there was no significant difference in the occurrence of these effects between the groups receiving melatonin or a placebo. The authors therefore concluded that there were no adverse effects associated with short-term administration of melatonin (3 months) in this range of doses, but considered that the data on long-term toxicity were insufficient.
A study assessed the toxicity of melatonin administered for 28 days to 30 healthy volunteers, at a dose of 10 mg/d. Ten other participants received a placebo. In the group receiving melatonin, 14 people (47%) presented with headaches. The same symptom was reported in the placebo group by three out of 10 people (30%), leading to a non-significant difference between the two groups.
A follow-up study, whose objective, was to assess the efficacy and safety of long-term melatonin treatment in prepubertal children with chronic sleep disorders. The average duration of melatonin treatment was around three years at an average dose of mg/d (from 0.3 mg/d to 10 mg/d). Thirty-eight per cent of these children reported having regular headaches. Two cases (4%) of weight gain were also reported. The study did not include a control group and the doses of melatonin received by the children with these adverse effects were not specified.
The occurrence of headaches has been reported in other publications where the melatonin doses were between 2 mg/d and 10 mg/d. For these studies, either no data on the significance of the occurrence of this effect were available, or this occurrence was not significant. The vasodilatory action of melatonin has been put forward as the mechanism responsible for this effect.

Sleepiness/fatigue

A randomised placebo-controlled study examining the effects of 3 mg/d of melatonin taken for four months on sleep, mood and hot flushes in post-menopausal breast cancer survivors reported cases of fatigue and sleep disorders. Four out of the 48 participants in the group treated by melatonin (8%) withdrew from the trial because of these adverse. No statistical analysis was performed of the relative occurrence of these effects between the treated group and the placebo group.
In a study, 17 cases of sleepiness were reported as an adverse effect in the group of 30 people (57%) treated with 10 mg/d of melatonin for 28 days. Six out of 10 people (60%) reported this effect in the placebo group, leading to a non-significant difference between the two groups.
In a publication, without a control group, the efficacy and safety of administering 0.3 mg/kg/d of melatonin for three months in the preventive treatment of migraine in children, 14 out of 60 children (23%) presented with daytime sleepiness, which resulted in three of them discontinuing treatment. The effects disappeared two or three weeks after stopping melatonin.
Many other publications dealing with the efficacy and safety of melatonin, administered over several days, weeks or months, have listed sleepiness as an adverse effect felt by the participants. The melatonin doses used in these tests were between 0.05 mg/d and 10 mg/d. In the majority of studies, either the occurrence of sleepiness was not significant compared to a placebo, or no data on the significance of the occurrence were available.
Digestive effects
Gastrointestinal disorders are adverse effects frequently reported following the administration of melatonin. Indeed, many cases have been observed in different studies where melatonin was administered for several days, weeks or months, at doses ranging from 0.1 mg/d to 10 mg/d. However, the occurrence of these effects was generally the same in the placebo group, when there was one. In addition, for studies where several doses were tested, no data were provided on the melatonin dose responsible for the adverse effect.

Cardiovascular effects
One case of palpitations was reported in a study, funded by the pharmaceutical industry. A 68-year-old woman who had taken 2 mg/d of melatonin for several weeks experienced palpitations. This effect was considered to be probably linked to melatonin. This person had a history of palpitations.
In the study, designed to assess the efficacy and safety of 0.3 mg/kg/d of melatonin for three months in the preventive treatment of migraine in children, a moderate hypotension was observed in two children (4%). In the absence of a control group, the significance of the occurrence of this effect could not be assessed.
Lower melatonin concentrations than in healthy subjects have been identified in people suffering from conditions of cardiovascular origin such as high blood pressure, congestive heart failure and ischaemic heart disease, or after an acute myocardial infarction.
As part of the marketing authorisation application for Circadin®, the pharmaceutical laboratory analysed the cardiovascular parameters of 38 patients with disorders of this type. Two milligrams of melatonin per day for four weeks did not modify heart rate or blood pressure in these patients.

Neurological effects
Migraine

A study, conducted without a placebo control, whose aim was to assess the effect of 3 mg of melatonin on sleep disorders, fatigue and pain in 21 patients with fibromyalgia. One woman left the study following the onset of migraine headaches after taking melatonin. A link between the consumption of melatonin and the onset of migraine was established due to the disappearance of symptoms after the cessation of treatment and their recurrence on its reintroduction.
Several studies have shown that plasma concentrations of endogenous melatonin or urinary concentrations of 6-sulphatoxymelatonin are lower in migraine sufferers.
A case, reported, of a 37-year-old man who, for more than 15 years, experienced four to six migraine attacks with aura per year in relation to the withdrawal of exogenous melatonin. The authors of this article suggest that the migraine attacks may be associated with a reduction in melatonin concentration caused by the withdrawal of exogenous melatonin intake. This case suggests that melatonin may play a role in the onset of migraine.

Epilepsy
Melatonin concentrations in patients with intractable epilepsy were lower than those in controls (subjects not presenting with sleep disorders or neurological conditions). However, they increased threefold in the 24 hours after seizures.
In a 1998 study, melatonin was administered to six children with neurological disabilities and chronic sleep disorders. The treatment consisted in administering 5 mg of melatonin by the oral route or via a gastrostomy tube at the patient's usual bedtime. In four of the treated patients (67%), a worsening or triggering of an epilepsy seizure was reported, leading to the study being stopped. The evolution of the seizures was systematically favourable after discontinuation of melatonin. In another study, a boy developed mild generalised epilepsy after receiving 5 mg/d of melatonin for four months.
Published case of a 21-year-old woman suffering from uncontrolled epilepsy, whose epileptiform activity was measured by magnetoencephalography 45 minutes after being administered 3 mg of melatonin. The results indicated an increase in epileptiform activity and the patient reported having experienced four brief seizures in the afternoon, each lasting a few seconds.

Restless legs syndrome
One study suggested that melatonin, by inhibiting dopamine transmission, could aggravate the symptoms associated with restless legs syndrome. Three mg of melatonin administered at 19:00 to eight subjects suffering from primary restless legs syndrome, in order to study the impact of the increase in circulating concentrations of exogenous melatonin on motor symptoms. These symptoms were aggravated in all subjects receiving the exogenous melatonin. The authors reiterated, however, that the main limitation to this study was the small number of people included.

Psychiatric effects
Nightmares
Nightmares occurring after taking melatonin are among the effects frequently reported in the literature. This effect was reported, for example, for a dose of 3 mg/d for 4 months in postmenopausal women or in children after a regular dose (from 2-3 times per week to several times per year) of 0.5 mg/d to 10 mg/d of melatonin for 1 to 57 months.
In the study 1 mg/d of melatonin was administered for three days to 19 healthy subjects. No adverse effects were reported except for abnormal dreams in one subject who, moreover, reported an increase in psychosocial stress factors at the time of the experiment due to personal circumstances independent of the study.

Agitation/mood
A randomised, double-blind placebo-controlled trial to determine the individual or combined impact of bright light and melatonin (2.5 mg/d for an average duration of 15 months) on cognitive decline, mood, behaviour and sleep disturbances in 189 elderly people, 87% of whom have dementia. The results show that melatonin alone negatively affected the mood of participants according to the observations of the caregivers. The authors of this article concluded that the long-term use of melatonin by the elderly can only be recommended in combination with light, to counteract its adverse effects on mood.
A randomised, double-masked, placebo-controlled study whose aim was to assess the effectiveness and safety of melatonin administered for 12 weeks in the treatment of severe sleep problems in children (146 children aged 3 to 15 years) with neurodevelopmental disorders. The children in the treated group started with a melatonin dose of mg/d, which was then increased to 2, 6 or 12 mg/d according to their response to the treatment. Sixteen out of the 70 children in the group treated by melatonin (23%) reported changes in mood, versus 17 out of 76 in the placebo group (22%). Thirteen children (19%) presented with increased excitability in the treated group, compared with 16 (21%) in the placebo group. No formal statistical tests were conducted to assess the significance of these effects.
Three cases of patients with an intellectual disability treated by various psychotropic drugs, in whom treatment with melatonin was associated with an increase in agitation. The daily doses involved were 2.5 mg, 6 mg and 10 mg. In each case, the effects lessened after discontinuation or a decrease in the dose of melatonin. The authors suggest that melatonin should be used with caution in people with an intellectual disability or mental disorders, especially those with a history of agitation.
A randomised placebo-controlled study on 51 children with chronic sleep disorders related to an intellectual disability. For 4 weeks, individuals aged 6 years or over received either 5 mg of melatonin in a quick-release tablet or a placebo every day at 19:00. Individuals under 6 years of age received a daily dose of 2.5 mg of melatonin at 18:00. In the treated group, five out of 29 individuals (17%) presented with increased crying during the day and agitation. These effects were not observed in the placebo group.

Depression
A study conducted on six patients with major primary depression and two patients with Huntington disease. They received varying doses of melatonin either orally, divided into four equal daily doses, or intravenously, once or twice a day for 3 to 12 days. The oral doses could go up to 1600 mg/d. The intravenously-administered dose could go up to 250 mg/d. This study showed an exacerbation of the depression, and the study was discontinued in view of melatonin's negative role in the depression of the patients included in the study. The doses used in this study were far higher than those typically found in the literature.
A case, reported of acute psychosis occurring in a person who appeared to have consumed a high dose of melatonin (around 30 mg) in combination with fluoxetine (10 mg). The authors of the case study suggested that the patient's psychotic episode was the consequence of a possible interaction between melatonin and fluoxetine.

Dermatological and allergic effects
These types of effects are very rarely reported in the literature. One article described the appearance of two independent cases of penile eruption in men aged 35 and 42 years who had consumed the same product containing 3 mg of melatonin. The lesions disappeared over the next 10 days, without any sequelae.

In a study on the long-term (1 to 57 months) effectiveness and safety of 0.5 to 10 mg/d of melatonin in children with attention-deficit disorder and chronic sleep-onset insomnia, observed a change in skin pigmentation in two children (2%).
The study described above, assessing the effectiveness and safety of melatonin in the treatment of severe sleep problems in 146 children with neurodevelopmental disorders, reported 11 cases (16%) of skin rash in the group treated with 2, 6 or 12 mg/d of melatonin for 12 weeks, compared with 8 cases (11%) in the placebo group. No statistical tests were conducted to assess the significance of this effect.
In a randomised, double-blind, placebo-controlled study conducted in 72 children suffering from chronic sleep disorders, receiving 0.05, 0.1 or 0.15 mg/kg/d of melatonin or a placebo for a week, 15 children (21%) presented with redness in the cheeks, ears and eyes within an hour of administration. The redness in the cheeks was reported in the three melatonin dose groups with a higher frequency for the group receiving the highest dose.

Uro-nephrological effects
The only uro-nephrological effects reported in the literature concern the effects of melatonin on urination or cases of nocturnal incontinence. Other cases of night incontinence occurred after long-term administration of 0.5 mg to 10 mg/d of melatonin to children with attention-deficit disorder and chronic sleep-onset insomnia.

Effects on inflammatory or autoimmune diseases
One case of autoimmune hepatitis occurring after consumption of melatonin was published. A publication reported the development of autoimmune hepatitis in a 50-year-old man, one month after starting consumption of 8 mg of ramelteon (a melatonin receptor agonist). A case of a woman suffering from Crohn's disease and treated with corticosteroids and sulfasalazine, was described. In April 2000, the patient decided to take 3 mg capsules of melatonin before bedtime. Four days later, she began to feel the symptoms of the active phase of Crohn's disease (diarrhoea, abdominal cramps). Twenty-four hours after discontinuing melatonin, there was a complete remission of symptoms. The authors concluded that in Crohn's disease and probably in other immune dysfunction diseases, the secretion of various cytokines (IL-2 and IL-12) induced by melatonin may exacerbate the symptoms of these diseases. The same team also published the case of a 56-year-old man suffering from ulcerative colitis treated by corticosteroids and sulfasalazine, who presented with the symptoms of the active phase of his disorder two months after beginning consumption of 3 mg/d of melatonin. Initially, the melatonin was continued and the corticosteroid doses increased. Because the symptoms had not ceased, the patient was hospitalised and the melatonin treatment was discontinued. Twenty-four to 48 hours later, the patient was in full remission. Serum concentrations of endogenous melatonin are higher in patients with rheumatoid arthritis than in healthy subjects.

Effects on glucose and insulin metabolism
In a single-blind placebo-controlled study including 21 healthy women, Rubio-Sastre et al. observed a decrease in tolerance during glucose tolerance tests after administration of 5 mg of melatonin. Effects on insulin secretion (for the tests carried out in the morning) and on the sensitivity to it (evening) were identified. The authors concluded as to a possible interaction between melatonin and glucose tolerance, particularly in subjects predisposed to a glucose intolerance, and suggested that melatonin should not be taken at mealtimes.

Two long-term studies (5 and 6 months) were conducted by a laboratory, as part of the marketing authorisation application for Circadin®, including a total of 80 people with type 2 diabetes and suffering from insomnia. No deleterious influence on glycaemic control was found for this population at a dose of 2 mg/d.

Overall safety profile of melatonin

Examined controlled studies of oral melatonin supplementation in humans when they presented any statistical analysis of adverse events. Of the fifty articles identified (2337 adults taking 1 – 10 mg oral melatonin, or placebo, for a minimum of 3 days), twenty-six found no statistically significant adverse events, while twenty-four articles reported on at least one statistically significant adverse event. Adverse events were generally minor, short-lived and easily managed, with the most commonly reported adverse events relating to fatigue, mood, or psychomotor and neurocognitive performance. A few studies noted adverse events relating to endocrine (e.g. reproductive parameters, glucose metabolism) and cardiovascular (e.g. blood pressure, heart rate) function, which appear to be influenced by dosage, dose timing and potential interactions with antihypertensive drugs. Oral melatonin supplementation in humans has a generally favourable safety profile with some exceptions. Most adverse effects can likely be easily avoided or managed by dosing in accordance with natural circadian rhythms.

Adverse reaction data from other systematic review) showed that of the total 35 studies included in the analysis, 15 included information on adverse events. No serious adverse events were reported. One study reported that adverse events occurred, but did not describe them, and two reported no adverse events occurred at all. The most common adverse events were headache and somnolence. Palpitations and abdominal pain were each reported in two studies. The remaining adverse events were report infrequently, and each occurred in only one of the multiple studies: nasopharyngitis, arthralgia, tachycardia, dizziness, nausea, vomiting, nightmares, difficulty swallowing and breathing, hypnotic activity, heavy head, heartburn, flatulence, swelling of arms/legs, sweating/hot flash, exanthema, sleeping difficulties, depression, problems with the rectal probe, and sleep walking.

Another review on the safety of melatonin documents that melatonin is safe for short-term use, even when given in extreme doses. Mild adverse effects, such as dizziness, headache, nausea and sleepiness have been reported in levels corresponding to placebo treatments. Final conclusions concerning long-term safety of melatonin are limited by a general lack of randomized, double blind, placebo-controlled studies, and methodical weaknesses in the reporting of possible adverse effects. However, the sparse data available suggest no serious adverse effects, even with long-term use.

Another review investigated the safety of higher doses of melatonin in adults. Randomised controlled trials investigating high-dose melatonin (≥10 mg) in human adults over 30 years of age were included. 79 studies were identified with a total of 3861 participants. Studies included a large range of medical conditions. Overall, only four studies met the pre-specified low risk of bias criteria for meta-analysis. In that small subset, melatonin did not cause a detectable increase in serious adverse events (Rate Ratio = 0.88 [0.52, 1.50], p = 0.64) or withdrawals due to adverse events (0.93 [0.24, 3.56], p = 0.92), but did appear to increase the risk of adverse events such as drowsiness, headache and dizziness (1.40 [1.15, 1.69], p < 0.001). Overall, there has been limited adverse event reporting from high-dose melatonin studies. Based on this limited evidence, melatonin appears to have a good safety profile.

The British National Formulary of March 2022 lists (alphabetically) the following adverse effects for melatonin:

Common or very common: arthralgia, headaches, increased risk of infection, pain.

Uncommon: Anxiety, asthenia, chest pain, dizziness, drowsiness, dry mouth, gastrointestinal discomfort, hyperbilirubinaemia, hypertension, menopausal symptoms, mood altered, movement disorders, nausea, night sweats, oral disorders, skin reactions, sleep disorders, urine abnormalities, weight increased.
Rare or very rare: Aggression, angina pectoris, arthritis, concentration impaired, crying, depression, disorientation, electrolyte imbalance, excessive tearing, gastrointestinal disorders, haematuria, hot flush, hypertriglyceridaemia, leucopenia, memory loss, muscle complaints, nail disorder, palpitations, paraesthesia, partial complex seizure, prostatitis, sexual dysfunction, syncope, thirst, thrombocytopenia, urinary disorders, vertigo, vision disorders, vomiting
Frequency not known: angioedema, galactorrhoea, hyperglycaemia

The cumulative data is sufficient to conclude that there are no particular safety concerns with short term use, as in the management of jet lag.

Provided the dose recommendations for the proposed product are adhered to, in respect of timing and the maximum recommended dose of 6 mg for up to a maximum of 5 days, the safety profile is favourable. Drowsiness and reduced alertness are the main risks. Warnings are in place in the product information in regard to driving and operating machinery.

IV.6 Risk Management Plan (RMP)

The Applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations was recommended for these applications.

V USER CONSULTATION

Full colour mock-ups of the Patient Information Leaflets (PILs) were provided with the applications in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified from the literature. Extensive clinical experience with melatonin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflets (PILs) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**