Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Melatonin 3 mg film-coated tablets

melatonin

PL 25258/0379

Glenmark Pharmaceuticals Europe Limited

LAY SUMMARY

Melatonin 3 mg film-coated tablets
melatonin

This is a summary of the Public Assessment Report (PAR) for Melatonin 3 mg film-coated tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Melatonin tablets in this lay summary for ease of reading.

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

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

Melatonin tablets 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 do Melatonin tablets work?
Melatonin tablets contain the active substance melatonin. 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 tablets can help restore the normal day-and-night rhythm and reduce the symptoms.

How are Melatonin tablets used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (by mouth).

The recommended dose for adults and elderly is 1 tablet daily for a maximum of 5 days. When the effect of Melatonin tablets is inadequate, 2 tablets can be taken simultaneously.

The first dose should be taken on arrival at destination at the patient’s usual bed-time. Intake on the following days should also be at their usual bedtime. The tablets should not be taken before 20:00 hr or after 04:00 hr.

The tablets 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 tablets.

Melatonin tablets may be taken for a maximum of 16 treatment periods per year.

The patient must talk to a doctor if they do not feel better or if they feel worse after 5 days.

For further information on how Melatonin tablets are used, refer to the PIL and Summary of

Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine 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 tablets 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 tablets are a safe and efficacious short-term treatment for jet-lag in adults.

What are the possible side effects of Melatonin tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC 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.

The most common side effects with Melatonin tablets (which may affect up to 1 in 10 people) are headache and drowsiness.

Why were Melatonin tablets approved?
It was concluded that the data provided from literature references had shown that Melatonin tablets are effective in the short-term treatment of jet-lag in adults. Furthermore, the well-established use of the active substance Melatonin tablets 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 tablets?
A Risk Management Plan (RMP) has been developed to ensure that Melatonin tablets are 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 tablets, how these risks can be minimised, any uncertainties about Melatonin tablets (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 tablets.

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 tablets

A marketing authorisation for Melatonin tablets was granted in the United Kingdom (UK) on 14 February 2024.

The full PAR for Melatonin tablets follows this summary.

This summary was last updated in December 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 application for Melatonin 3 mg film-coated tablets (PL 25258/0379) could be approved.

Melatonin 3 mg film-coated tablets are indicated for short-term treatment of jet-lag in adults.

The active substance is melatonin, which is a hormone and antioxidant. Melatonin secreted by the pineal gland is involved in the synchronisation of circadian rhythms to the diurnal light-dark cycle. Melatonin 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.

The pharmacological mechanism of action of 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.

This application was approved under Regulation 54 of The Human Medicines Regulation 2012, as amended (previously Article 10a of Directive 2001/83/EC, as amended), as a well-established use application. 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 this product at all sites responsible for the manufacture, assembly and batch release of this product.

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

A national marketing authorisation was granted in the United Kingdom (UK) on 14 February 2024.

II QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains 3 mg of the active substance melatonin.

In addition to melatonin, this product also contains the following excipients:
Core tablet: Microcrystalline cellulose, maltodextrin, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate.

Film-coating: Hypromellose, macrogol and titanium dioxide.

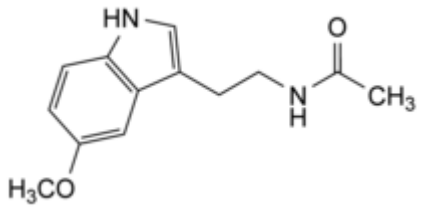
The finished product is packaged in Alu-Alu or PVC-PVDc blister packs, in a pack size of 30 tablets.

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*-[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: White to slightly yellowish powder
Solubility: Slightly soluble in water, soluble in ethanol (96 per cent), sparingly soluble in ethyl acetate and practically insoluble in heptane

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 a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a 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 product.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

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

Satisfactory batch formulation data have been provided for the manufacture of the product, 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 no special storage conditions, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
This application was submitted under Regulation 54 of The Human Medicines Regulation 2012, as amended, as a well-established use application. No new non-clinical studies were submitted, as the data submitted for this application is in the form of literature references. The literature review provided is satisfactory.

III.2 Pharmacology
No new pharmacology data were submitted, and none were required for this application. The Non-clinical Overview provides an adequate review of the available published data on the non-clinical pharmacology of melatonin. Any gaps in the published literature have been adequately justified.

III.3 Pharmacokinetics
No new non-clinical pharmacokinetic data were submitted, and none were required for this application. The Non-clinical Overview provides an adequate review of the available published data on the non-clinical pharmacokinetics of melatonin. Any gaps in the published literature have been adequately justified.

III.4 Toxicology
No new toxicology data were submitted, and none were required for this application.
The Non-clinical Overview provides an adequate review of the available published data on the non-clinical toxicology of melatonin. Any gaps in the published literature have been adequately justified.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a product 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 Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation 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 current formulation presents composition similarity to other currently authorised oral tablets containing melatonin. Critical Quality parameters such as *in vitro* dissolution have been investigated and are comparable between test and marketed products.

The Applicant has demonstrated a bridge can be established between their product and those presented in the literature and/or currently available in the UK market.

IV. 2 Pharmacokinetics

The pharmacokinetic (PK) properties of melatonin are well-known. Oral immediate-release (IR) melatonin is rapidly absorbed from the small intestine. The time to reach C_{max} (T_{max}) is 15-90 min (mean, ~50 min). Oral bioavailability of melatonin is low, i.e., ~15 %. Increase in the maximum concentrations (C_{max}) can be expected if melatonin is taken with food. Even though it is not expected to affect the efficacy or safety, melatonin is not recommended to be taken concomitantly with food. Exogenous melatonin passes the blood-brain barrier (BBB) and is distributed in all body fluids and tissues.

Melatonin is mainly metabolised in the liver by the CYP1A2 with contribution from CYP1A1 and CYP2C19, yielding 6-hydroxymelatonin; the sulphate conjugate of the latter is a principal metabolite, but is inactive. Metabolism is very rapid, with metabolite levels rising within minutes. Metabolites are excreted in the urine. The elimination half-life ($t_{½\beta}$) is approximately 45 min. The kinetics of oral melatonin are linear over range 0.1-8 mg.

Absorption

A thorough critical reviewing of the available PK studies involving oral administration of melatonin formulations in humans has been performed. An overview of published PK studies utilising melatonin is presented in Table 1 below.

Table 1. Mean PK variables reported in the public domain scientific literature after single oral administration of melatonin formulations at low doses ranging from 0.1 to 100 mg to healthy volunteers.

Dose (mg)	Dosage form	Time of intake	Dosing condition	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2\beta}$ (min)	AUC (ng×min/ml)	Cl/F (L/min)	F (%)
2	Gelatin capsule	10:00	Fasted	2.80	15	32	222.72	-	-
			Fed	6.80	30	-	482.16	-	
2	Corn oil preparation		Fasted	3.50	30		237.18		
			Fed	4.40	30	40	349.56		
5	Tablet	Morning	Fasted	12.40	37.5	51.9	1179 (*)	-	-
2mg	Sustained-release tablet	10:00	Fasted	0.43	96		151.62		
			Fed	0.48	156		144.30		
2	Tablet	07:00-09:00	Fasted	2.18	52	61	237.77 (*)	-	14
4				5.77	60	65	530.57 (*)	-	16
0.5	-	-	-	-	-	47	-	-	33
0.1	Capsule	11:45	-	0.05	135	-	12.79	-	-
0.3				0.12	135	-	27.59	-	-
1				0.40	135	-	95.94	-	-
0.25	Oral solution (male)			0.24	23	36	14.16		
0.25	Oral solution (female)			0.62	23	45	42.08		
0.4	Oral (25% dose IR and 75% dose CR)			0.41	78	108	95.70	6.32	
4.0	Oral (25% dose IR and 75 % dose CR)			4.00	90	126	727.4	7.97	
5	IR	10:00	-	2.18	-	-	372	-	-
6	Tablet IR	08:30	-	4.48	60	106	-	3.08	-
6	Tablet IR	09:00	Fasted	1.80	60	37	138(*)	132.50	-
5	Capsule IR	-	-	4.82	30	38	256.89(*)	-	-
10	Controlled release			3.82	45	48	507.91(*)		
				4.07	210	50	595.40(*)		
0.5	Capsule	0.5 h before sleep	-	0.84	30	42	134.28	-	-
		4 h after bedtime		0.70	60	42	78.81	-	-
5	Slow release			8.77	167	91	2.3×10^3	3.09	
6	Tablet	09:00	Fasted (different age)	16.76	30	46	1,180	8.44	-
				16.44	53	52	1,240	9.88	-
3	Capsule	09:30	-	0.68	60	68.4	99.78	-	-
1	Capsule powder			0.80	60		90.5	-	-
	Soft-gelatine capsule	-	-	2.62	60	-	283.2		
3	Capsule powder			2.40	40		269.1		
2.5	Capsule	23:00	-	3.17	540	-	635.15	-	-
3	-	09:30	-	3.56	20	-	-	-	-
25mg	Capsule	09:30	Fed smoking	0.64	90		102.41		

			Fed non-smoking	1.86	90		294.00		
100mg	Gelatine capsule	09:15		101.16	60	41			
80	Gelatine capsule	11:00				48	27.87×10^3		
3x80		11:00, 12:00, 13:00					31.30×10^3		
0.3	Capsule	0.5 h before sleep	-	0.20	60	-	42.71	-	-
5	Capsule			2.05	120	-	426.47	-	-
0.3	Capsule	21:00	-	0.11	49.8	-	29.94	-	-
0.3	Gelatine capsule	11:00	-	0.17	48	-	26.51	-	-
				0.26	45	-	35.75	-	-
0.1	Capsule	0.5 h before bedtime	-	0.08	120	-	29.94	-	-
0.3				0.22	120	-	57.36	-	-
3				1.37	120	-	466.74	-	

Abbreviations: Cmax, maximal plasma/serum concentration; Tmax, time to maximal plasma/serum concentration; t½β, elimination half-life; AUC, area-under-the-curve plasma/serum concentrations (up to the last measurable concentration, AUC0-t, unless marked with (*), which denotes AUC0-inf), Cl/F, apparent clearance; F, bioavailability.
The symbol (−) refers to studies not reporting the pre-defined PK variable, or not reporting a mean/median-data value of the specific variable.

From a thorough analysis of the above tabulated data, following oral administration of different oral solid melatonin-formulations:

- C_{max} ranged from 0.05 ng/ml (0.1-mg dose, capsule, IR dosage form) to 101.16 ng/ml (dose 100 mg, gelatine-capsule, IR). Taking into account all preparations, the mean (±standard deviation [SD]) C_{max} was 5.24 (±15.31) ng/ml, while taking into account only the IR preparations, this was 5.64 (±16.65) ng/ml.
- T_{max} for the oral formulations ranged from 15 min (2 mg, gelatine-capsule, IR) to 540 min (2.5 mg, IR capsule). Taking all values together both from sustained-release and from IR formulations, the mean (±SD) T_{max} after oral administration was 83 (±85) min. Eliminating the sustained-release formulations, the mean (±SD) Tmax of the IR ones was 76 (±88) min. A T_{max} of melatonin being ~ 30-50 min seems well-established from the literature.
- t½β ranged from 32 min (2 mg, gelatine capsule, IR) to 126 min (4 mg, oral tablet preparation with 25% dose IR release and 75% dose controlled-release), or when taking into consideration only IR formulations, 106 min (6 mg, tablet IR). The mean (±SD) for all oral preparations was 57 (±25) min while only for the IR ones, this was 49 (±17) min. A t½ of melatonin being ~45min is well-established in the literature.
- AUC ranged between 12.79 ng×min/ml (0.1 mg capsule, IR dosage form) to 31.30×103 ng×min/ml (3×80 mg, gelatine capsule) or 27.87×103 ng×min/ml (80 mg, gelatine capsule). Taking all formulations into consideration, the mean (±SD) was 1.7×103 (±6.2×103) ng×min/ml while only for immediate release formulations mean (±SD) was 1.9×103 (±6.8×103) ng×min/ml.

Here, it is necessary to focus on those administering oral melatonin in an IR formulation at daily doses of 0.5-5.0 mg. The isolation of these studies (Table 2) was based on evidence of posology from clinical trials of melatonin for the treatment of jet lag.

Table 2. Mean PK variables reported in the public domain scientific literature after single oral administration of melatonin IR formulations in conventional dosage forms; the doses ranged from 0.5 to 5 mg.

Dose (mg)	Dosage form	Time of intake	Dosing condition	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2\beta}$ (min)	AUC (ng×min/ml)	F (%)
2.0	Gelatine capsule	10:00	Fasted	2.80	15	32	222.72	13.6
			Fed	6.80	30	-	482.16	13.7
5.0	Tablet	Morning	Fasted	12.40	37.5	51.9	1179.23(*)	28.9
2.0	Tablet	07:00-09:00	Fasted	2.18	52	61	237.77(*)	**14.4**
4.0				5.77	60	65	530.57(*)	**16.2**
0.5	-	-	-	-	-	47	-	**33.0**
1.0	Capsule	11:45	-	0.40	135	-	95.94	11.7
5.0	-	10:00	-	2.18	-	-	372	9.1
5.0	Capsule	-	-	4.82	30	38	256.89(*)	6.3
0.5	Capsule	0.5 h before sleep	-	0.84	30	42	134.28	32.9
		4 h after bedtime		0.70	60	42	78.81	19.3
3.0	Capsule	09:30	-	0.68	60	68.4	99.78	4.1
1.0	Capsule powder	-	-	0.80	60	-	90.5	11.1
	Soft gel capsule	-	-	2.62	60	-	283.2	34.7
3.0	Capsule powder	-	-	2.40	40	-	269.1	11.0
2.5	Capsule	23:00	-	3.17	540	-	635.15	31.1
3.0	-	09:30	-	3.56	20	-	-	-
5.0	Capsule	0.5 h before sleep	-	2.05	120	-	426.47	10.4
3.0	Capsule	0.5 h before bedtime	-	1.37	120	-	466.74	19.0

Cmax: maximal plasma/serum concentration, Tmax: time to maximal plasma/serum concentration, t½ β: elimination half-life, AUC: area-under-the-curve plasma/serum concentrations (up to the last measurable concentration, AUC0-t, unless marked with (*), which denotes AUC0-inf), Cl/F: apparent clearance, F: bioavailability, The symbol (−) refers to studies not reporting the pre-defined PK variable, or not reporting a mean/median-data value of the specific variable. Almost F(%) values were calculated based on the study where 2 mg of melatonin IV bolus were administered and resulted in a mean (±SD) AUC0-inf 1,631.61 (425.74) ng×min/ml. F (%) values in bold were directly retrieved from the cited reference.

Therefore, after oral administration of IR melatonin formulation in doses ranging from 0.5-5.0 mg:

- C_{max} ranged from 0.40 ng/ml (1.0 mg) to 12.40 ng/ml (5.0 mg), with a mean (±SD) value 3.1 (±2.9) ng/ml.
- T_{max} ranged from 15 min (2.0 mg) to 540 min (2.5 mg), with a mean (±SD) value 86 (±122) min. However, by eliminating this extreme high value that could represent an outlier, the maximum value of T_{max} is 135 min (1.0 mg) and the mean (±SD) value 58 (±36) min. It should be noted that the latter mean is also in accordance with the mean T_{max} value referred in the literature which is 30-50 min. Moreover, as observed after reviewing the efficacy studies the best outcome is achieved when melatonin is administered 30-60 min before bedtime, which coincides with its T_{max}.
- t½β ranged from 32 min (2.0 mg) to 68 min (3.0 mg), with a mean (±SD) value 49 (±12) min. A t½β of melatonin being ~45 min is well-established in the literature.

- AUC ranged from 78,8 ng×min/ml (0.5 mg) to 1,179.23 ng×min/ml (5.0 mg), with mean (±SD) value 329.6 (±273.1) ng×min/ml.
- F (%) bioavailability (estimated from the literature data), ranged from 4.1% (3.0 mg) to 34.7% (1.0 mg) with a mean (±SD) value 16.9 (±9.4)%.

After having distinguished only the most relative PK studies with the intended dosing and formulation, it can be observed that variability of PK parameters is relatively high. Data from studies conducted at other strengths can be extrapolated to the 3 mg dose, since the pharmacokinetics are linear. However, mainly due to the well-known first-pass effect that melatonin undergoes, the bioavailability is rather low. The variable bioavailability of oral melatonin is therefore not related to the differing instant release formulations but is due to the variability in the high first pass metabolism of melatonin.

Two studies investigating the PKs of melatonin after administration of an oral solution IR formulation have been identified in the scientific literature as well (Table 3). One was performed in critically ill patients and the other one in healthy volunteers.

Table 3. Mean PK variables reported in the public domain scientific literature after single oral administration of melatonin oral solution doses ranging from 0.25 to 10 mg.

Dose (mg)	Volunteers	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2}$ (min)	AUC (ng·min/ml)	Cl/F (L/min)
10	Critically ill	14.97	30	88	1.80×10^3	5.85
0.25	Healthy males	0.24	23	36	14.16	-
0.25	Healthy females	0.62	23	45	42.08	-

A study estimated the absolute bioavailability of melatonin in 12 young healthy volunteers after administration at midday, on 2 separate occasions, i.e., 0.23 mg by IV infusion and 0.25 mg by oral solution. Melatonin PKs were compared with those obtained after the administration of 0.23 mg melatonin by IV infusion (at a rate of 250 ml/h). In healthy males, PK parameters were C_{max}=0.24 ng/ml, T_{max}=23 min, t½=36 min, AUC0-inf=14.16 ng×min/ml and the absolute bioavailability mean (±SD) was 8.6 (±3.9) %. In the female subjects, the PK parameters were C_{max}=0.62 ng/ml, T_{max}=23 min, t½=45 min, AUC0-inf = 42.08 ng×min/ml, and the absolute bioavailability mean (±SD) was 16.8 (±12.7)%. The absolute bioavailability of melatonin ranged from 1% to 37% with a mean (±SD) of 8.6 (±3.9)% for males and 16.8 (±12.7)% for females.

It is interesting to note that the bioavailability of the oral solution is comparable to those of the IR solid forms (see above), being within the range, and approaching the mean. T_{max} is lower compared to what it was observed for the solid IR forms, as is expected from an oral solution, not having the limiting step of dissolution. Moreover, it might also be of concern the fact that the main variables establishing bioequivalence, i.e., AUC and Cmax, are also lower than the values obtained with solid dosage forms, even though this could be due to the very low dose administered. In any case, melatonin has been also approved as oral solution formulation (Melatonin Colonis PAR) claiming the same indication (jet lag) and posology as the solid formulations.

Overall, a generally low bioavailability (F) of oral melatonin has been documented in a number of studies and was confirmed by the assessment conducted above, fluctuating mainly from 3-36%. Bioavailability presented a significant intra-individual variability. Moreover, the administration of different formulations also probably accounts for the differences observed in bioavailability. It is generally agreed that the low bioavailability is caused by a considerable first-pass metabolism in the liver. The other PK parameters (C_{max} and AUC) displayed extensive variation within and between studies. The variations may obviously relate to interindividual differences in drug absorption, distribution, metabolism, and elimination but may also be confounded by substantial variability in study designs/analytical methods. Other reasons accounting for these variations are probably low absorption from the GI tract, an extensive first-pass metabolism in the liver or a combination of both. Melatonin undergoes a substantial first-pass metabolism in the liver. Therefore, factors affecting liver metabolism can lead to significant changes on its bioavailability.

The PKs of melatonin from other routes of administration were also reviewed in order to gain better insight on how the route of administration affects its bioavailability.

Table 4. Mean PK variables reported in the public domain scientific literature after IV, transdermal, intranasal and transmucosal administration of melatonin.

Dose (mg)	Dosage form	C_{max} (ng/ml)	T_{max} (min)	$T_{1/2}$ (min)	AUC (ng·min/ml)	Cl/F (L/min)	Vd (L)
2.1	Transdermal	-	8.58h	-	-	-	-
10	IV bolus	221.5	-	42.3	8,997.63	-	1.6
100	IV bolus	1,251.5	-	46.2	54,685.97	-	2.0
20	Transdermal	-	2.8-8h	-	-	-	-
100			1.1-6h				
5	Sublingual spray	17.20	42.5min	54.0	-	-	-
8	Transdermal	-	13h	-	-	-	-
0.5	Transmucosal		474min				
0.0005 mg/kg	IV prepubertal	-	-	40	15.05	3.30	185
	IV pubertal			47	18.00	2.70	173
	IV adults			47	22.61	2.03	135
2	IV	96.85	-	60	1.63×10^3	-	-
0.23	IV infusion (250 ml/h) male	1.25	113	36	15.29	1.57	73.1
0.23	IV infusion (150ml/h) female	1.69	110	41	21.84	1.09	53.8
0.005	IV bolus			28	5.40	0.97	35
0.02	IV (10ml/h) infusion	0.072	-	45	-	0.97	63
0.4	Intranasal	-	5	-	-	-	-
0.2	IV		10				
3.6	Transdermal nanoparticle gel in 9 cm2 skin area	-	15h	7.5h	-	-	-

Routes of administration avoiding first-pass effect (IV, intranasal) result in increased bioavailability in comparison to oral dosage forms. Transdermal administration of melatonin might be used optimally in a local application, rather than a systemic application, due to slow skin release.

Dose-dependency of bioavailability in the 0.5-5.0 mg oral dose rage
Based on the above considerations, the above reported PK studies were separated into 4 basic categories in order to roughly investigate the variability of the PK parameters where doses of the same magnitude were administered.

Table 5. Mean PK variables reported in the public domain scientific literature after single oral administration of melatonin IR formulations doses 0.5-1.0 mg to healthy volunteers.

	Dose (mg)	**C_{max} (ng/ml)**	**T_{max} (min)**	**$t_{1/2\,\beta}$ (min)**	**AUC (ng×min/ml)**	**F (%)**
	0.5	-	-	47	-	33
	1.0	0.40	135		95.94	11.7
	0.5	0.84	30	42	134.28	32.9
		0.70	60	42	78.81	19.3
	1.0	0.80	60		90.50	11.1
		2.62	60	-	283.20	34.7
Min		0.40	30.00	42,00	78.81	11.10
Max		2.62	135.00	47,00	283.20	34.70
Mean		**1.07**	**69.00**	**43.67**	**136.55**	**23.78**
SD		**0.88**	**39.12**	**2.89**	**84.58**	**11.08**

Abbreviations: Cmax: maximal plasma/serum concentration, Tmax: time to maximal plasma/serum concentration, t½β: elimination half-life, AUC: area-under-the-curve plasma/serum concentrations (up to the last measurable concentration, F: bioavailability.

Table 6. Mean PK variables reported in the public domain scientific literature after single oral administration of melatonin IR formulations doses 2.0-2.5 mg to healthy volunteers.

	Dose (mg)	**Cmax (ng/ml)**	**Tmax (min)**	**t1/2 β (min)**	**AUC (ng×min/ml)**	**F (%)**
	2.0	2.80	15	32	222.72	13.6
		6.80	30	-	482.16	13.7
	2.0	3.50	30		237.18	14.5
		4.40	30	40	349.56	21.4
	2.0	2.18	52	61	237.77	14.4
	2.5	3.17	540	-	635.15	31.1
Min		2.18	15.00	32.00	222.72	13.60
Max		6.80	540.00	61.00	635.15	31.10
Mean		**3.81**	**116.17**	**44.33**	**360.76**	**18.12**
SD		**1.64**	**207.97**	**14.98**	**167.10**	**7.02**

Abbreviations: Cmax: maximal plasma/serum concentration, Tmax: time to maximal plasma/serum concentration, t½β: elimination half-life, AUC: area-under-the-curve plasma/serum concentrations (up to the last measurable concentration, F: bioavailability.

Table 7. Mean PK variables reported in the literature after single oral administration of melatonin IR formulations dose 3.0 mg to healthy volunteers.

Reference	**Dose (mg)**	**C_{max} (ng/ml)**	**T_{max} (min)**	**$t_{1/2\,\beta}$ (min)**	**AUC (ng×min/ml)**	**F (%)**
	3.0	2.40	40		269.10	11.0
	3.0	3.56	20	-	-	-
	3.0	1.37	120	-	466.74	19,0
Min		1.37	20.00	0,00	269.10	11.00
Max		3.56	120.00	0,00	466.74	19.00
Mean		**2.44**	**60.00**		**367.92**	**15.00**
SD		**1.10**	**52.92**		**139.75**	**5.66**

Abbreviations: Cmax: maximal plasma/serum concentration, Tmax: time to maximal plasma/serum concentration, t½β: elimination half-life, AUC: area-under-the-curve plasma/serum concentrations (up to the last measurable concentration, F: bioavailability.

Table 8. Mean PK variables reported in the scientific literature after single oral administration of melatonin IR formulations doses 5.0 mg to healthy volunteers.

	Dose (mg)	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2\,\beta}$ (min)	AUC (ng×min/ml)	F (%)
	5.0	12.40	38	52	1179.23	28.9
	5.0	2.18	-	-	372.00	9.1
	5.0	4.82	30	38	256.89	6.3
	5.0	2.05	120	-	426,47	10.4
Min		2.05	30.00	38.00	256.89	6.30
Max		12.40	120.00	51.90	1179.23	28.90
Mean		**5.36**	**62.50**	**44.95**	**558.65**	**13.68**
SD		**4.86**	**49.94**	**9.83**	**419.72**	**10.29**

Abbreviations: Cmax: maximal plasma/serum concentration, Tmax: time to maximal plasma/serum concentration, t½β: elimination half-life, AUC: area-under-the-curve plasma/serum concentrations (up to the last measurable concentration, F: bioavailability.

Although it cannot be concluded with certainty, in a dose range of 0.5-5.0 mg IR, both C_{max} and AUC seem to be dose dependent, while absolute bioavailability seems not to be affected by dose.

Food effect

The food effect could be formulation dependent, since it was noticed in a sustained-release 2 mg melatonin formulation, however, another literature review has depicted a study that has determined plasma concentrations of melatonin under fed and fasting conditions. Melatonin concentrations were higher in the fed state compared to fasted state for both solid and liquid formulations tested, however T_{max} was close (for the solid capsules) and the same (for the liquid form) for both prandial states. Most approved SmPCs for similar products recommend avoidance of food consumption 2 hours before to 2 hours after taking melatonin; this will be included in the SmPC for this product.

Distribution

Melatonin is not strongly or extensively bound to plasma proteins, therefore protein binding effects on PKs should not be expected to be significant. Indeed, the in vitro plasma protein binding of melatonin is about 60.0%. Melatonin is mainly bound to albumin, α1-acid glycoprotein and high-density lipoprotein (HDL). The level of melatonin binding appears to be constant over range of different serum concentrations. Literature data indicate that melatonin is distributed in all body fluids and is accessible at all tissues. The mean binding of melatonin to erythrocytes is 49.0 %.

Melatonin reaches all tissues of the body within a very short period. Its t½ is bi-exponential, with a first distribution t½ of 1.4 min and a second of 28.4 min. Distribution from serum to saliva and passing through the BBB is rapid. Melatonin released to the CSF via the pineal recess attains, in the 3rd ventricle, concentrations up to 20-30 times higher than in blood. These concentrations, however, rapidly diminish with increasing distance from the pineal, thus suggesting that melatonin is taken up by brain tissue. IV bolus administration of [14C]-melatonin was shown to rapidly cross the BBB, interact with brain structures and quickly disappear from the brain, which suggests rapid diffusion and turnover.

In a human PET study performed with [11C]-melatonin in a healthy volunteer, analysis of tracer kinetics showed maximum activity in the brain at 8.5 min following injection, which was different from the curve observed for the plasma radioactivity (maximum at 3.5 min). This result confirmed that melatonin readily crosses the BBB and that 6-sulphatoxymelatonin is the main plasma metabolite. In this study, the distribution of tracer as a function of time, failed to reveal any specific binding.

It has been estimated that the mean steady state volume of distribution (Vd,ss) in healthy adult volunteers, following an IV infusion of D7-melatonin, to be 0.98 L/kg distribution. No gender difference in the Vd,ss normalised to body weight was observed; 0.99±0.063 L/h/kg and 0.97±0.13 L/h/kg in male and female subjects, respectively.

Previous studies have demonstrated that melatonin levels during pregnancy in maternal, foetal and umbilical cord blood closely correlate following ingestion of clinically used oral doses.

An early study compared the melatonin concentrations in blood samples collected from 5 subjects every 2-4 h over a 26-h period, with the melatonin concentrations in saliva samples and with the total amount of 6-sulphatoxymelatonin excreted in the urine during 2-h periods. There was significant correlation between serum and salivary melatonin concentrations ($r=0.81$, $P<0.001$), and between serum melatonin concentrations and 6-sulphatoxymelatonin excretion rates ($r=0.72$, $P<0.001$). These results demonstrated that both salivary melatonin concentrations and urinary 6-sulphatoxymelatonin excretion rates are reliable indices of serum melatonin levels that can be used for monitoring melatonin circadian rhythmicity.

Metabolism and elimination

Circulating melatonin is metabolised primarily in the liver where it is first hydroxylated in the C6 position to 6-hydroxymelatonin by cytochrome P450 mono-oxygenases (isoenzymes CYP1A2, CYP1A1 and, to a lesser extent, CYP1B1) and thereafter conjugated with sulphate to be excreted as 6-sulphatoxymelatonin and excreted in urine. Glucuronide conjugation is extremely limited. CYP2C19 and, at lower rates, CYP1A2 also demethylate melatonin to N-acetylserotonin, being otherwise its precursor.

A study used a panel of 11 recombinant human P450 isozymes to investigate for the first time the 6-hydroxylation and O-demethylation of melatonin. CYP1A1, CYP1A2, and CYP1B1 all 6-hydroxylated melatonin, with CYP2C19 playing a minor role. These reactions were NADPH-dependent. CYP2C19 and, to some extent CYP1A2, O-demethylated melatonin. The Km (μM) and Vmax (kcat, pmol/min/pmol P450) for 6-hydroxylation were estimated as 19.2±2.01 and 6.46±0.22 (CYP1A1), 25.9±2.47 and 10.6±0.32 (CYP1A2), and 30.9±3.76 and 5.31±0.21 (CYP1B1). These findings confirm the suggestion of others that CYP1A2 is probably the foremost hepatic P450 in the 6-hydroxylation of melatonin and a single report that CYP1A1 is also able to mediate this reaction. However, this is the first time that CYP1B1 has been shown to 6-hydroxylate melatonin. The 50% inhibitory concentration (IC50) for the CYP1B1-selective inhibitor (E)-2,4,3',5'-tetramethoxystilbene was estimated to be 30 nM for melatonin 6-hydroxylation by recombinant human CYP1B1. Comparison of brain homogenates from wild-type and cyp1b1-null mice revealed that 6-hydroxylation of melatonin was clearly mediated to a significant degree by CYP1B1. CYP1B1 is not expressed in the liver but has a ubiquitous extrahepatic distribution and is found at high levels in tissues that also accumulate either melatonin or 6-hydroxymelatonin, such as intestine and cerebral cortex, where it may assist in regulating levels of melatonin and 6-hydroxymelatonin.

The metabolism in extrahepatic tissues exhibits substantial differences. Neural tissues, including the pineal gland and retina, contain melatonin-deacetylating enzymes, which are either specific melatonin deacetylases or less specific aryl acylamidases. Since eserine-sensitive acetylcholinesterase has an aryl acylamidase side activity, melatonin can be deacetylated to 5-methoxytryptamine in any tissue carrying this enzyme. Melatonin can be metabolised non-enzymatically in all cells, and also extracellularly, by free radicals and a few other oxidants. It is converted into cyclic 3-hydroxymelatonin when it directly scavenges two hydroxyl radicals. Studies have shown that repeated melatonin administration does not alter the metabolic profile of the hormone.

In a study, a markedly increased AUC for the ratio of 6-sulphatoxymelatonin to melatonin in plasma after oral as compared with IV administration (13±13 vs. 1±1) was found, which can be explained only if one assumes that there was considerable first-pass hepatic extraction following oral administration (which converts melatonin to its metabolite before it enters the systemic circulation), giving rise to the conversion of melatonin to 6-sulphatoxymelatonin and thereby decreasing the bioavailability of the hormone.

A substantial fraction of melatonin is metabolised to kynuramine derivatives in the brain. This is of interest as the antioxidant and anti-inflammatory properties of melatonin are shared by these metabolites, N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and, with considerably higher efficacy, N1-acetyl-5-methoxykynuramine (AMK). AFMK is produced by numerous non-enzymatic and enzymatic mechanisms; its formation by myeloperoxidase appears to be important in quantitative terms.

Elimination

6-Sulphatoxymelatonin, the primary metabolite of melatonin, accounts for around 90% of the dose excreted in urine. The other main metabolite results from O-demethylation of melatonin, yielding N-acetylserotonin. Approximately 2% of the exogenous melatonin is excreted in an unchanged form. No figures are provided as to the extent of urine excretion of the secondary metabolite, mainly the glucuronide conjugate of 6- hydroxymelatonin. A t½β of ~45 min has been documented in several studies in a wide range of doses, up to 100 mg IV. This parameter may also be described by first-order elimination kinetics and is independent of dose and route of administration. In addition, approximately 1% of blood melatonin is excreted in urine without being metabolised. A positive correlation between AUC of melatonin and 6-sulphatoxymelatonin has been demonstrated in urine. The measurement of the main melatonin metabolite in urine seems to provide a robust, simple and reliable assessment of melatonin secretion. Over 90% of the administered radioactivity (β-[14C] melatonin) was recovered in the first 24-h urine sample and the remainder in the next 24 h.

Following IV infusion of 23 µg D7-melatonin, total body clearance in healthy males and females was 1.27±0.20 L/h/kg and 1.18±0.222 L/h/kg, respectively. The t½ of melatonin following single IV and oral doses in healthy volunteers has been reported to be ~1 h. In another study, the t½β has been reported as 43.6 min after IV administration in human subjects. It has also been determined that the t½ following an IV infusion to be 36.0 and 41.4 min in male and female subjects, respectively, and after oral dosing, 36.0 and 45.0 min, respectively.

In a population PK turnover and surge-function study, describing the circadian disposition of melatonin in healthy male subjects, the t½β was estimated to be 2.7 h, i.e., longer than 0.5-1.0 h reported after exogenous IV and oral melatonin administration to healthy adults. This difference may reflect the continuous formation and release of melatonin while hormone synthesised earlier was undergoing elimination from the bloodstream, thereby leading to an underestimation of the terminal phase slope.

Special populations

- Impaired renal function

Literature data indicate that there is no accumulation of melatonin after repeated dosing (3 mg for 5 – 11 weeks) in patients on stable haemodialysis. However, as melatonin is primarily excreted as metabolites in the urine, plasma levels of melatonin metabolites can be expected increase in patients with more advanced renal impairment.

There is only limited experience regarding the use of melatonin in patients with renal impairment. Caution should be exercised if melatonin is used by patients with renal impairment. Melatonin 3 mg film-coated tablets is not recommended for patients with severe renal impairment.

- Impaired hepatic function

Limited data indicate that daytime endogenous blood melatonin concentration is markedly elevated in patients with liver cirrhosis, probably due to reduced clearance (metabolism) of melatonin. Serum T½ for exogenous melatonin in cirrhosis patients was double that of controls in a small study. As the liver is the primary site of melatonin metabolism, hepatic impairment can be expected to result in increased exposure to exogenous melatonin.

Melatonin 3 mg film-coated tablets is not recommended in patients with moderate or severe hepatic impairment.

- Critically ill patients

Critically ill patients exhibit reduced melatonin secretion, both in nocturnal peaks and basal daytime levels. Its early enteral absorption and daily PKs were determined in 2 cohorts of 6 high-risk patients in a prospective trial. Following enteral administration, pharmacological levels were already reached in 5 min with a serum Cmax after 16 min (half-absorption time: 3 min and 17 s). The serum Cmax observed was 11,040 pg/ml and the disappearance rate indicated a t½β of 1 h and 34 min. Serum melatonin levels decreased significantly after midnight; pharmacological levels were maintained up to 10 h following administration. Critically ill patients exhibited reduced melatonin secretion and despite the critical illness, the oral bioavailability was satisfactory; serum levels after oral administration showed basically unchanged intestinal absorption, while disappearance rate was slower than reported in other studies in healthy volunteers.

- Pinealectomy

The PKs of melatonin during the daytime has been studied in 4 healthy subjects after a bolus IV injection of 5 or 10 µg/person and after a 5 h infusion of 20 µg/person in 6 healthy subjects. In addition, a pinealomectomised patient whose nocturnal plasma melatonin had been abolished was investigated after the IV infusion (once during the night and once during the day).

The clearance of melatonin from blood showed a biexponential decay. The PK parameters in the two studies were similar, except for the disappearance rate constant beta and the apparent Vd,ss. Supplementary peaks or troughs were superimposed on the plateau and the falling part of the profile. They were not due to stimulation of endogenous secretion, because they were also seen in the pinealomectomised patient. During the melatonin infusion, the plasma hormone level reached a steady-state after 60 and 120 min, and when it was equal to the nocturnal level. The infusion regime may be valuable in replacing blunted hormonal secretion in disease states.

- Exercise

A study investigated the effects of a heavy resistance exercise session (RES) with the oral daytime ingestion of melatonin, in a randomised, double-blind controlled study with 10 healthy male subjects who undertook an 80 min intensive hypertrophic RES for major muscles of the lower and upper extremities. The subjects were studied on 2 occasions receiving either melatonin (6 mg) or placebo (6 mg) in random order 60 min before each RES. Blood samples were taken from an antecubital vein both in fasting conditions in the morning and before RES (pre 60 min, pre 0 min), during RES (middle) and after RES (post 0 min, post 15 min, post 30 min, post 60 min). Melatonin concentration in serum increased significantly ($P<0.05$-0.001) in the melatonin group following oral ingestion of melatonin and was elevated at every time point after that. The C_{max} of 1,171.3±235.2 pg/ml was reached in 60 min at pre 0. Serum melatonin increased slightly but significantly ($P<0.05$) also in the placebo group just before RES, in the middle of RES and after RES (post 0, post 15). There were large differences ($P<0.01$-0.001) in the serum melatonin concentration between the groups at all timepoints.

- Elderly

Night-time endogenous melatonin plasma concentration is lower in the elderly compared to young adults. Limited data for plasma- Tmax, Cmax, elimination half-life (T½), and AUC following ingestion of immediate-release melatonin do not indicate significant differences between younger adults and elderly persons in general, though the range of values (inter-individual variability) for each parameter tend to be greater in the elderly.

As the pharmacokinetics of melatonin (immediate release) is comparable in young adults and elderly persons in general, no specific dosage recommendations for elderly persons are provided.

- Pregnancy and lactation

Melatonin has protective actions on both the foetus and the mother during pregnancy. It can easily cross the placenta to enter the foetal circulation leading the photoperiodic information to the foetus. During pregnancy there is a high metabolic demand for oxygen, which leads to a higher reactive oxygen species (ROS) production and, consequently, oxidative stress. The placenta is a major source of oxidative stress because it is rich in poly-unsaturated fatty acids. Spontaneous abortion and recurrent pregnancy loss have been associated with systemic oxidative stress. Due to melatonin level increase, during gestation in normal pregnant humans, reducing the oxidative stress and abortion rate, melatonin has been suggested as a potential molecule to be administered throughout compromised pregnancy such as in pre-eclampsia and foetal undernutrition, both associated with oxidative stress. Melatonin levels were found to be decreased in severe pre-eclampsia. Some recent evidence has suggested supplements of melatonin to prevent pre-eclampsia in humans.

In a study, blood and milk samples were obtained between 14:00 and 17:00 h and again within 02:00-04:00 h from 10 nursing mothers 3-4 days after delivery. Melatonin in both fluids was beyond the limit of detection (<10 ng/L) during the day, whereas during the night, its concentration was 280±34 pmol/L in serum and 99±26 pmol/L in milk. In another study, 21 mothers collected breast-milk samples 5 times in a 24-h period on postpartum days 5-10. The median melatonin concentration in daytime milk (10:00-22:00 h) was 1.5 mg/L and the median concentration in nighttime milk (22:00-10:00) was 7.3 ng/L. No statistically significant difference was found between the breast milk of mothers with pre- and full-term infants.

One study found that breast-milk melatonin concentration was inversely correlated with breast-milk prolactin level and was higher in women experiencing fatigue in the morning. Five nursing mothers provided breast-milk samples every 2 h over a 24-h period. Melatonin was undetectable during the day, but began to rise at about 8 pm, reaching a peak at about 3 am, and then declining.

In 30 women who were 48-72 h postpartum, melatonin levels in colostrum averaged about 16 ng/L at noon and 36 ng/L at midnight. Another study found that melatonin colostrum levels measured between 01:00 and 03:00 between 48 and 72 h postpartum were higher in mothers who delivered vaginally (mean=266 ng/L) than in those delivering by elective (mean=205 ng/L) or emergency caesarean section (mean=167 ng/L). All differences between groups were statistically significant.

In studies in which exogenous oral melatonin was given to women, the resulting serum melatonin level was variable, but serum C_{max} ranged from 1.1 to 2.6 µg/L for each 1 mg administered. This would result in an average increase melatonin concentration in breast-milk from 0.4 to 1 µg/L for each 1 mg received, based on an average milk concentration of 35% of the maternal serum concentration. While the resulting concentrations would be higher than the typical physiologic C_{max} of 0.02 µg/L in milk, it would present a considerably lower dose to the infant than the 10-mg/kg melatonin dosages that have been safely administered to neonates.

Melatonin was analysed in 392 breast-milk samples from 98 healthy nursing mothers at 0-30 days postpartum. At 03:00, preterm colostrum had a higher average concentration than term colostrum, i.e., 28.67 and 25.31 ng/L, respectively. Melatonin levels were numerically, but not statistically, higher in transitional and term milk at 03:00. The lowest levels of melatonin in milk occurred at 09:00 and 21:00. A study compared daytime and nighttime melatonin colostrum and milk levels in mothers who had an elective caesarean section (n=18) to those who had a vaginal delivery (n=21). Nighttime melatonin levels were higher in colostrum, transitional and mature milk in both groups, with nighttime melatonin ranging from 10.9 to 17.5 ng/L higher than daytime levels. Colostrum melatonin levels were higher in mothers who had an elective cesarean section (average=30.3 ng/L) than in mothers who had a vaginal delivery (average 14.7 ng/L).

A study of 8 breastfed and 6 formula-fed infants found different patterns of the melatonin metabolite, 6-sulphatoxymelatonin, in urine. Breastfed infants had a sinusoidal excretion pattern with a peak at 6 am and a trough at 6 pm. Formula-fed infants had a simple increase in the metabolite that was at baseline between about 8 pm and 4 am with a peak at about noon.

Interactions

Interaction studies have been performed in adults. Melatonin is metabolised mainly by the hepatic cytochrome P450 CYP1A enzymes, primarily CYP1A2. Therefore, interactions between melatonin and other active substances as a consequence of their effect on CYP1A enzymes are possible. For instance, CYP1A2 inhibitors (such as quinolones) may increase systemic melatonin levels, wherease CYP1A2 inducers (like carbamazepine and rifampicin) may reduce plasma concentrations of melatonin. Melatonin may enhance the sedative effect of benzodiazepines (e.g., midazolam, temazepam) and non-benzodiazepine hypnotics (e.g., zaleplon, zolpidem, zopiclone). Melatonin may affect the anticoagulation activity of warfarin.

Carbamazepine: CYP1A2 inducers, such as carbamazepine, may reduce melatonin plasma concentration.

Citalopram: Active surveillance identified a 19-year-old male taking citalopram, nortriptyline and oxycodone concomitantly and who experienced severe sedation when melatonin was added to this regimen. *In vitro* analysis involving several melatonin products showed product-dependent inhibition of CYP1A2, CYP2C19 and CYP3A7. The adverse event (AE) of sedation was likely due to a primary PK interaction between melatonin and citalopram; although mechanistically, interactions affecting cytochrome P450-mediated metabolism may have occurred with all of these health products. A PD interaction may also be possible.

Selective serotonin re-uptake inhibitors (SSRIs): Fluvoxamine is known to inhibit CYP1A2 potently, and to some extent also CYP2C19, whereas citalopram is without such an effect. Also, CYP enzymes are involved in the hepatic metabolism of melatonin. In a study, 7 healthy subjects participated in 3 different experiments, performed in random order 6-8 days apart. Placebo, citalopram 40 mg and fluvoxamine 50 mg were given orally (at 16:00 h) in experiments A, B and C, respectively. Plasma citalopram levels were measured repeatedly in experiment B, and plasma fluvoxamin concentrations in experiment C. Fluvoxamin augmented the AUC0-20h of melatonin by a factor of 2.8 compared with the effect of placebo ($P<0.01$), whereas citalopram was without significant effect. More melatonin was excreted in the urine after ingestion of fluvoxamin than after placebo. In contrast, citalopram did not influence melatonin excretion. According to the SmPCs of the approved melatonin tablet formulations, caution is indicated in patients treated with fluvoxamine, since this agent increases melatonin levels (17-fold higher AUC and 12-fold higher serum Cmax) due to inhibition of melatonin metabolism via CYP1A2 and CYP2C19. This combination should be avoided.

Zopiclone and temazepam: The effects of single oral doses of zopiclone (7.5 and 15 mg) and temazepam (20 mg) on nocturnal secretion of melatonin were investigated in 8 healthy male volunteers, in a single blind, placebo-controlled crossover study. Each dose was separated by at least a 1-week washout period. Both temazepam and zopiclone tended to reduce the amount of melatonin secreted, as determined by the AUC. The differences from placebo were not statistically significant ($F\ 3.31 = 1.07$, $P>0.1$). Similarly, a repeated measures analysis of variance on the plasma AUCs did not show any statistically significant differences between drugs and placebo ($F\ 3.28 = 1.15$, $P>0.1$). There was no evidence from this study of a phase shifting effect of the drugs used. The reasons for the lack of effect on melatonin may be due to the differences in potency of the interaction of these drugs with the GABA-benzodiazepine-chloride ion channel.

Oral contraceptives (OCs): The effect of OCs on melatonin metabolism was studied in 29 subjects genotyped for CYP1A2 SNP g.-163C>A polymorphism. Plasma melatonin and 6-hydroxymelatonin concentrations were measured after a 6-mg melatonin dose. The mean melatonin AUC and C_{max} values were 4- to 5-fold higher in OC users than in non-OC users ($P<0.0001$), whereas the weight-adjusted clearance was significantly lower in OC users ($P<0.0001$). No significant difference in melatonin PKs between the genotypes and no additional effect by the genotype on the OC-induced increase in melatonin exposure were evident. Melatonin exposure had no significant effect on the state of alertness of the subjects. Overall, a significant inhibitory effect of OCs on CYP1A2-catalysed melatonin metabolism was seen; thereby, OC use can alter CYP1A2-phenotyping results.

Oestrogens: Melatonin downregulates the circulating levels of gonadal oestrogens and acts as an antioestrogen with mechanisms of action different to those of the commercially available antioestrogens and inhibits aromatase expression in human breast cancer cells. The metabolism by CYP1A1 isoenzymes are inhibited and CYP1A2 increases melatonin levels. Caution should be exercised in patients on oestrogens (e.g., contraceptive or hormone replacement therapy), which increase melatonin levels by inhibiting its metabolism by CYP1A1 and CYP1A2.

Caffeine: A 3-phase crossover study in 12 healthy volunteers has examined whether caffeine (200 mg single dose), taken 12 or 24 h prior to melatonin intake, would affect the results of CYP1A2 phenotyping results as assessed by a spot sample melatonin concentration 1.5 h after oral intake of 6-mg melatonin. The influence of the CYP1A2*1F polymorphism on the phenotyping results was also examined by combining the present material with another 12 subjects from a previous study. Caffeine, co-administered 12 or 24 h prior to melatonin intake, did not have any significant effect on the 1.5-h melatonin concentration ($P=0.086$ for ANOVA), but in 2 volunteers, about 4 times increase in melatonin concentration was observed after caffeine intake 12 h (but not 24 h) before phenotyping with melatonin. Also, individuals homozygous for the CYP1A2*1A allele had clearly higher 1.5-h melatonin concentration compared with the *1F/*1F or the *1F/*1A genotypes. Abstinence from caffeine for 24 h prior to melatonin intake should be enough to overcome the possible confounding effect of caffeine on the CYP1A2 phenotyping with melatonin. Melatonin may be a sensitive probe to detect phenotypic differences with regard to CYP1A2*1F polymorphism. Melatonin might be, thus, advantageous for CYP1A2 phenotyping compared to the standard probe caffeine. When caffeine (3×200 mg) was coadministered with melatonin (6 mg), the Cmax and AUC of melatonin were increased on average by 142% ($P=0.001$, CI on the difference 44, 80%) and 120% ($P<0.001$, CI on the difference 63, 178%), respectively. The inhibitory effect of caffeine was more pronounced in non-smokers and in individuals with the *1F/*1F genotype.

Cimetidine: Cimetidine increases plasma melatonin concentration (via inhibition of CYP1A2) by inhibiting the metabolism of melatonin.

Methoxypsoralen (MOP): Results from a clinical study have demonstrated that 8-MOP (or 5-MOP) intake is followed by correlated changes in melatonin levels and an independent decrease in serum 6-sulphatoxymelatonin levels, suggesting a competitive inhibition of hepatic melatonin metabolism.

Smoking: Polycyclic aromatic hydrocarbons in cigarette smoke induce cytochrome P450(CYP)1A2, which is involved in the hepatic metabolism of melatonin; this suggests that habitual smokers may have low serum melatonin levels during smoking compared with a non-smoking period. Eight habitual smokers were tested on two occasions; they had smoked prior to the 1st occasion but had not smoked for 7 days prior to the 2nd. Each test was divided into two parts. The 1st part spanned the night between 20:00 h and 08:00 h and the 2nd part was performed the subsequent day. At 09:30 h, 25 mg of melatonin was ingested orally. Endogenous serum AUCs of melatonin were similar during the two periods. Oral administration of melatonin induced supraphysiological levels of the hormone in serum. Moreover, exogenous serum AUCs of melatonin were significantly smaller before than after smoking abstinence (7.34±1.85 vs. 21.07±7.28 nmol/L×h; $P<0.02$; means±standard error of the mean [SEM]).

Effects on endogenous melatonin
Melatonin is metabolised in the liver by CYP1A2. A study investigated whether patients with different CYP1A2 activity would have different nocturnal serum melatonin levels. Hence, serum concentrations of melatonin were determined every 2nd h during the night in 12 healthy subjects and the AUCs for melatonin were calculated; caffeine clearance was determined in advance. As known, caffeine clearance reflects CYP1A2 activity. This made it possible to evaluate whether a relationship prevails between endogenous AUCs of melatonin and CYP1A2 activity. If CYP1A2 is important for the metabolism of melatonin, one would expect to find an inverse correlation between the AUCs of melatonin and caffeine clearance. However, such correlation did not exist in the current study (Rs= –0.021, not significant). Since AUC of endogenous melatonin depends not only on melatonin elimination by CYP1A2 but also on melatonin secretion, it is possible that an increased melatonin secretion counterbalances an increased hepatic metabolism of the hormone. If so, this could explain why the AUCs of melatonin and clearance of caffeine values were not inversely correlated in this study.

Caffeine and bright light effects on nighttime melatonin in women were tested during the luteal phase of the menstrual cycle (n=30) or the pseudo-luteal phase for OC users (n=32). In particular, participants were randomly assigned to receive either bright (5,000 lx) or dim room light (<88 lx) between 20:00 and 08:00 h under a modified constant routine protocol; then, half the subjects in each lighting condition were administered either caffeine (100 mg) or placebo in a double-blind manner at 20:00, 23:00, 02:00 and 05:00 h. Results showed that melatonin levels were reduced throughout the duration of bright light exposure for all women. Caffeine reduced the onset of melatonin levels for women in the luteal phase, but it had little effect on melatonin levels for OC users. The results for women in the luteal phase of the menstrual cycle are consistent with our previous findings in men. OCs may alter the effects of caffeine on nighttime melatonin levels.

A study examined the effects of acute administration of the GABAergic drug, sodium valproate, on nocturnal blood melatonin levels in healthy subjects (4 men and 3 women, aged 24-33 years), receiving orally 400 or 800 mg sodium valproate, or placebo (randomly, in a double-blind design) at 19:00 h. As compared to placebo, sodium valproate, at both 400 and 800 mg, significantly suppressed nocturnal blood melatonin levels, the higher dose being slightly more effective than the lower one. The maximum suppression coincided with the highest plasma levels of valproic acid. Thus, endogenous GABA may participate in the modulation of the activity of the human pineal gland.

IV.3 Pharmacodynamics

Mechanism of action

Melatonin, a derivative of tryptophan, is a natural indoleamine hormone produced (from serotonin) by the pineal gland of humans and other mammals; chemically, it is not related to the steroid or peptide hormones. Tryptophan is first 5-hydroxylated (by tryptophan hydroxylase) and then decarboxylated (by aromatic L-amino acid decarboxylase) to form 5-hydroxytryptamine or serotonin. During daylight hours, the serotonin in pinealocytes tends to be stored, and is unavailable to enzymes (monoamine oxidase [MAO] and the melatonin-forming enzymes) that would otherwise act on it. With the onset of darkness, post-ganglionic sympathetic outflow to the pineal increases, and the consequent release of norepinephrine onto pinealocytes, causes stored serotonin to become accessible for intracellular metabolism. At the same time, norepinephrine activates the enzymes (especially serotonin-N-acetyltransferase [SNAT], but also hydroxyindole-O-methyltransferase [HIOMT]) that convert serotonin to N-acetylserotonin and then to melatonin. Consequently, pineal melatonin level rises manifold and then diffuses out of the pineal gland into the blood stream and CSF, rapidly raising human plasma melatonin levels from about 2-10 to 100-200 pg/ml.

Melatonin binds to MT type 1A, which then acts on adenylate cyclase and the inhibition of a cyclic adenosine monophosphate (cAMP) signal transduction pathway. Melatonin not only inhibits adenylate cyclase, but it also activates phospholipase (PL) C; this potentiates the release of arachidonate.

By binding to MTs 1 and 2, the downstream signalling cascades have various effects in the body. The MTs are G protein-coupled receptors (GPCRs) and are expressed in various tissues of the body. There are two subtypes of the receptor in humans, the MT1 and MT2. Melatonin and MT-agonists, on the market or in clinical trials, all bind to and activate both receptor types, causing numerous physiological processes. MT1 receptors are expressed in many regions of the CNS, i.e., SCN, hippocampus, substantia nigra, cerebellum, central dopaminergic pathways, ventral tegmental area and nucleus accumbens. They are 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 MTs 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 cAMP, and then progressing to less protein kinase A (PKA) activity, which in turn hinders the phosphorilation of cAMP responsive element-binding protein (CREB binding protein) into P-CREB. MT1 receptors also activate PLC, affect ion channels and regulate ion flux inside the cell. The binding of melatonin to MT2 receptor inhibits adenylyl cyclase which decreases the formation of cAMP. It also hinders guanylyl cyclase and therefore the forming of cyclic guanosine monophosphate (cGMP). Binding to MT2 receptors probably affects PLC which increases PKC activity. Activation of the receptor can lead to ion flux inside the cell.

Melatonin has a role in ocular pathophysiology. In addition to the pineal gland, melatonin synthesis is carried out in several ocular structures. Moreover, specific MTs have been located in the retina, cornea, ciliary body, lens, choroid and sclera, which suggests that cells in these tissues may be targets for melatonin action.

Melatonin acts by 4 mechanisms in mammals, i.e., (i) binding to MTs in plasma membrane;

(ii) binding to intracellular proteins such as calmoduline; (iii) binding to orphan nuclear receptors; (iv) antioxidant effect.

Melatonin interacts with intracellular proteins named calmoduline, calreticulin and tubulin. Calmoduline is an intracellular secondary messenger. Melatonin directly antagonises binding of calcium to calmoduline. The antiproliferative effect in cancer may be related to this.

Retinoid-related Orphan nuclear hormone receptor family (RZR/ROR) is responsible for the immunomodulatory effects of melatonin. Interleukin (IL)-2 and IL-6 are produced in mononuclear cells by this mechanism.

There are 3 different membrane receptors and 1 nuclear receptor. In humans, MTs are also detected in several organs, including brain and retina, cardiovascular system, liver and gallbladder, intestine, kidney, immune cells, adipocytes, prostate and breast epithelial cells, ovary/granulosa cells, myometrium, and skin.

- Melatonin receptor type 1a: MT1 (Mel1a, ML1a, MT1, MTNR1A)

It is encoded in human chromosome #4 and consists of 351 amino acids. MT1 constitutes adenylate cyclase inhibition by binding to various G-proteins. MT1 receptors are commonly found in human skin. During aging process and Alzheimer's disease, the expression of MT1 in SCN and cortex decreases. MT1 receptors reduce the neuronal discharge rate in SCN and suppress prolactin secretion.

- Melatonin receptor type 1b: MT2 (Mel 1b, ML1b, MT2, MTNR1B)

It is encoded in human chromosome 11 and consists of 363 amino acids. MT2 creates adenylate cyclase inhibition by binding to various G-proteins. Additionally, it inhibits the soluble guanylyl cyclase pathway. Through MT activation, adenylate cyclase inhibition occurs, and the production of cAMP is reduced.

In the skin, MT2s are located within normal and malign melanocytes and eccrine sweat glands. They inhibit gamma-aminobutyric acid (GABA) A receptor-related functions in the hippocampus in rats. In Alzheimer's disease, MT2 expression is reduced. MT2 receptors contribute to the pathophysiology and pharmacology of sleep disorders, anxiety, depression, Alzheimer's disease and pain, and are also involved in antidepressant activity. MT2 receptors are responsible for anxiolytic effects of melatonin. Pharmacological studies have revealed that MT2 regulates sleep, particularly non-rapid eye movement sleep (NREMS). MT2 ligands have more powerful hypnotic properties when compared to non-selective MT1/MT2 ligands.

- The MT3 subtype (Mel1c, MTNR1C) is not present in humans, but it is found in fish, amphibians and birds. In chicken, the rhythm of MT3 is the opposite of MT1 and MT2. Its level is highest at daytime and lowest at night-time. MT3 or else the enzyme quinone reductase 2 (QR2) belongs to the reductase group, involved in prevention from oxidative stress by inhibiting the electron transfer reactions of quinones. There is additional evidence for its involvement in regulation of intraocular pressure. MT3 is located in the liver, kidney, heart, lung, intestine, muscle and brown fat tissue.

- Retinoid-related Orphan nuclear hormone receptor family (RZR/RORα):

Via this receptor, melatonin binds to the transcription factors in nucleus which belong to retinoic acid receptor super-family.

• Melatonin-related Orphan receptor; 'X linked Orphan G-protein coupled' (GPR50: H9, ML1X) is an X-linked inherited receptor, binding to G-protein. It is the orthologue of MT3, which is found in non-mammalian living creatures. This receptor's gene is located on the X chromosome (Xq28) and consists of 618 amino acids. It is present in all mammalians including humans. It does not have the characteristics of binding to melatonin; however, it is effective in binding of melatonin to MT1. GPR50 is not present in birds and fish. It is located in the brain and periphery. Its natural ligand has not been defined yet. It was reported that a deletion mutant in GPR50 might have been associated with bipolar disorder and major depression. GPR50 has no affinity to melatonin; however, when it dimerises with MT1, it inhibits the melatonin signal. GPR50 also possesses other functions apart from melatonin; it interacts with neurite outgrow inhibitor (NOGO-A) and TIP60 (glucocorticoid receptor signal co-activator and histone acetyltransferase).

Primary pharmacology

In mammals, the SCN-activated, light-inhibited production of melatonin conveys the message of darkness to the clock and induces night-state physiological functions, for example, sleep/wake blood pressure and metabolism. Clinically meaningful effects of melatonin treatment have been demonstrated in placebo-controlled trials in humans, particularly in disorders associated with diminished or misaligned melatonin rhythms, for example, circadian rhythm-related sleep disorders, jet lag and shift work, insomnia in children with neurodevelopmental disorders, poor (non-restorative) sleep quality, non-dipping nocturnal blood pressure (nocturnal hypertension) and Alzheimer's disease. The diminished production of melatonin at the very early stages of Alzheimer's disease, the role of melatonin in the restorative value of sleep (perceived sleep quality) and its sleep-anticipating effects resulting in attenuated activation of certain brain networks are gaining a new perspective as the role of poor sleep quality in the build-up of β-amyloid, particularly in the precuneus, is unravelled. Melatonin may also promote sleepiness via its effects on peripheral vessels. It induces a vasodilation itself leading in turn to an increase of skin temperature which constitutes an effective signal for sleepiness. This last effect may be the prominent mechanism of action of exogenous melatonin.

Circadian regulation of sleep

The neurons of the major circadian clock, the SCN of the hypothalamus, are normally active during the day and slow down at night. The activation of SCN neurons has an inhibitory effect on the pineal gland, defining a nocturnal pattern of melatonin secretion. If SCN neurons are activated at night, e.g., by environmental light perceived by the retina, melatonin production declines. Melatonin, in turn, can acutely attenuate the activity of SCN. This action of melatonin is likely to support a normal decline in the activity of the SCN at night, further promoting melatonin secretion and contributing to an overall increase in the amplitude of circadian body rhythms. A temporal and functional interplay between melatonin and SCN, and their response to environmental light, promote a temporal alignment of multiple circadian body rhythms with each other (internal synchronisation) and with the periodic changes in the environment (external synchronisation). In addition to an acute inhibition of SCN activity, melatonin administration can also produce a shift in the circadian phase of SCN activity, either advancing or delaying its onset. The direction of the phase-shift depends on the time of melatonin treatment, i.e., administration of melatonin in the late afternoon can advance the circadian clock, while early-morning treatment can cause a phase delay. *In vitro* studies have suggested that a chronobiological effect of melatonin, i.e., the induction of circadian phase shift, is likely to be explained by its direct effect on SCN neurons via specific, most likely, MT2 receptor. Although the magnitude of the melatonin-induced phase shifts can vary between the species, the overall phenomenon appears to be well-conserved.

Such phase shifts in the circadian oscillation of SCN activity may change the physiological and behavioural rhythmicity of the entire organism, including the sleep-wake cycle, and can significantly affect the sleep quality in both nocturnal and diurnal species. In humans suffering from circadian sleep disorders, daily melatonin treatment can help to reinforce the circadian synchronisation with the environment and entrain the physiological rhythms to a 24-h cycle.

Older people typically exhibit poor sleep efficiency and reduced nocturnal plasma melatonin levels. The daytime administration of oral melatonin to younger people, in doses that raise their plasma melatonin levels to the nocturnal range, can accelerate sleep onset. The ability of similar, physiological doses to restore night-time melatonin levels and sleep efficiency in was examined insomniac subjects over 50 years of age. In a double-blind, placebo-controlled study, subjects who slept normally (n=15) or exhibited actigraphically confirmed decreases in sleep efficiency (n=15) received, in randomised order, a placebo and three melatonin doses (0.1, 0.3, and 3.0 mg) orally 30 min before bedtime for a week. Treatments were separated by 1-week washout periods. Sleep data were obtained by polysomnography on the last 3 nights of each treatment period. The physiologic melatonin dose (0.3 mg) restored sleep efficiency ($P<0.0001$), acting principally in the mid-third of the night; it also elevated plasma melatonin levels ($P<0.0008$) to normal. The pharmacologic dose (3.0 mg), like the lowest dose (0.1 mg), also improved sleep; however, it induced hypothermia and caused plasma melatonin to remain elevated into the daylight hours. Although control subjects, like insomniacs, had low melatonin levels, their sleep was unaffected by any melatonin dose.

Whether melatonin can facilitate phase shifts in a simulated night-work protocol has been tested in 32 subjects, slept in the afternoons/evenings before night work (a 7-h advance of the sleep schedule), who received melatonin (0.5 or 3.0 mg) or placebo before the 1st h of 8 afternoon/evening sleep episodes at a time when melatonin has been shown to phase advance the circadian clock. Melatonin produced larger phase advances than placebo in the circadian rhythms of melatonin and temperature. Average phase advances (±standard deviation [SD]) of the dim light melatonin onset (DLMO) were 1.7±1.2 h (placebo), 3.0±1.1 h (0.5 mg), and 3.9±0.5 h (3.0 mg). A measure of circadian adaptation, shifting the temperature minimum enough to occur within afternoon/evening sleep, showed that only subjects given melatonin achieved this goal (73% with 3.0 mg, 56% with 0.5 mg, and 0% with placebo).

A subsequent study, involving healthy adults (25 males and 19 females; aged 19-45 years), demonstrated that afternoon melatonin, morning intermittent bright light, and a gradually advancing sleep schedule advanced circadian rhythms almost 1 h/day, thus, producing very little circadian misalignment. In particular, there were 3 days of a gradually advancing sleep/dark period (wake time 1 h earlier each morning), bright light on awakening (four 30-min bright-light pulses of ~5000 lx alternating with 30 min room light <60 lx) and afternoon melatonin, either 0.5 or 3.0 mg melatonin timed to induce maximal phase advances, or matching placebo. According to the results, that there were significantly larger phase advances with 0.5 mg (2.5 h, n=16) and 3.0 mg melatonin (2.6 h, n=13), compared to placebo (1.7 h, n=15). There was no difference between melatonin doses. Subjects did not experience jet lag-type symptoms during the 3-day treatment.

In a double-blind placebo-controlled parallel-group study of a 27-day forced desynchrony paradigm with a 20-h scheduled sleep-wake cycle, 36 healthy adults (aged, 18-30 years; 21 men and 15 women) received orally either melatonin (0.3 mg or 5.0 mg) or placebo, 30 min prior to each 6.67-h sleep episode during forced desynchrony. Both melatonin doses improved polysomnographically determined sleep efficiency from 77% in the placebo group

to 83% for sleep episodes occurring during circadian phases when endogenous melatonin was absent. However, this remained below the average sleep efficiency of 88% observed during sleep episodes scheduled during the circadian night, when endogenous melatonin was present. Melatonin did not significantly affect sleep initiation or core body temperature. Melatonin appeared to maintain efficacy across the study and did not significantly affect percentages of slow-wave sleep or rapid eye movement (REM) sleep.

Secondary pharmacology

Relationship between plasma concentration and effect

Based on its mechanism of action as a chronobiotic, the response of the body to melatonin follows a phase-response curve (PRC), so that morning administration causes a delay, while evening administration causes an advance on circadian rhythms. This PRC is about 12 h out of phase with the PRC to light which causes a phase advance in the morning and a phase delay in the evening. The shift of the circadian rhythm induced as depicted in the PRC is a pharmacodynamic (PD) marker that may be considered indicative of melatonin's efficacy in the treatment of jet lag. A number of studies have investigated the PRC produced after administration of exogenous melatonin at a specific time and after subtraction of the baseline PRC estimated before administration. This is also supported by the fact that the observed differences on the effects of melatonin in relation to administration time are not due to differences in PKs, but probably in a difference in the concentration of endogenous melatonin and in the phase of circadian human rhythm.

Serum melatonin levels in normal humans are very low during most of the day (10 pg/ml) but increase significantly to a mean of 80 pg/ml (range, 30-120 pg/ml) between 02:00 and 04:00 morning hours and remain elevated during the normal hours of sleep, falling sharply to daytime values around 09:00 h. Melanotin doses of 0.1-0.3 mg taken during daytime generated melatonin C_{max} in serum within the normal nocturnal ranges of untreated people. Administration of such doses and higher ones produce measurable hypnotic effects independently of the circadian time signal synchronising action. This underlines the importance of administration time in relation to the desired effects. PK studies have shown that serum melatonin levels return to the basal level within 4 h after a 2-mg oral dose, while with an 80-mg oral dose, melatonin level increased from 17 pg/ml (basal level) to 25,800 pg/ml within 1 h and decreased to 203 pg/ml in 10 h. Unlike the sustained blood levels observed from endogenous release, oral doses produce a rapid increase in blood concentration followed by a rapid decrease.

In an attempt to investigate the potential dose-relationship when administering exogenous melatonin, a study evaluated the phase shift and the induced change in core body temperature. Following administration of 0.5- and 3.0-mg melatonin doses at the same clock times over 4 pulses (days), 3.0- and 3.9-h phase advances were observed, respectively. As for the shifting in the temperature minimum to occur within afternoon/evening was achieved by 73% of the volunteers receiving 3 mg and 56% of those taking 0.5 mg of melatonin. A previous study established a dose-response relationship with IR 0.5-5.0 mg melatonin, by evaluating the phase shift induced, sleep onset, sleep quality and the core body temperature (Table 9). In this study, in 6 healthy volunteers took a non-conventional oral dosage form consisting of a milk suspension of a corn-oil melatonin preparation.

Table 9. PK-PD relationship of melatonin

Dose (mg)	Administration time (h)	T_{max} (min)	C_{max} (pg/ml)	$t½_{\beta}$ (min)	Plasma concentration at maximum response (*) (pmol/L)	Phase advance (h)
0.05	17:00	30	118	64.8	~430	0.36
0.50		60	1,327	42.6	~4,300	0.69
5.00		30	18,495	70.2		1.43

Abbreviations: Cmax, maximal plasma/serum concentration; Tmax, time to Cmax; t½β, elimination half-life; AUC, area-under-the-curve plasma/serum concentrations; (*) Acute effects on core body temperature suggest that the half-maximal response occurs in these concentrations.

A study demonstrated that both 3 and 0.5 mg of melatonin induced a mean phase advance and a mean phase delay of the same magnitude, i.e., ~1.5 h. In addition, another study showed that 0.5 and 5.0 mg of IR melatonin were practically equally effective in alleviating jet lag, while 2 mg melatonin as a sustained-release formulation was less effective. The better results obtained with IR compared to sustained-release formulations were also observed in another study after administration of 3 mg melatonin as an IR, as a sustained release and as a formulation consisting of 25% IR+75% of sustained-release. Thus, IR formulations are more efficacious in the treatment of jet lag than controlled-release dosage forms.

As mentioned, the range of salivary melatonin levels is directly correlated with plasma levels; indeed, they are 27-32% of those measured in blood. Thus, measurements in saliva may be also indicative of melatonin PKs. In a study proving the efficacy of melatonin in resynchronisation after a 7-h eastward travel, salivary melatonin was measured before travel (control) and then, volunteers were divided into placebo, 5 mg IR melatonin, and 300 mg slow-release caffeine. Saliva melatonin control levels ranged between 0.14-409 pg/ml (mean, 30 pg/ml). The placebo group had saliva melatonin concentrations significantly higher starting 3 days post-flight. Both the melatonin and the caffeine group maintained the saliva melatonin and thus, plasma levels near to control levels almost for all days of the experiment (30 pg/ml measured at 07:00).

In a study, salivary samples contained >300 pg/ml melatonin 1 h after administration of 3 mg melatonin, which is in accordance with previous PK findings proving that the maximum levels of melatonin and thus maximum effects are noticed about 1 h post-dose. Thus, the plasma levels achieved with an IR dosage form about 1 h post-administration may be indicative of its efficacy (Table 10).

Table 10. Plasma concentrations produced 1 h after melatonin administration as a single IR oral formulation.

Dose (mg)	Plasma levels (pg/ml)
0.1	50
0.3	120
1.0	400
2.0	1900
10.0	6300
80.0	25800

However, there is no direct dose-response relationship, especially in terms of jet lag management or phase shifting, probably due to the inherent variability of circadian rhythms among humans. A non-linear dose response in melatonin PRC with only ~40% increased amplitude for a 500% larger dose has been demonstrated. Based on dose-response studies evaluating sleep onset, it was proved that melatonin receptors are saturated at levels >200 pg/ml, as doses from 0.3 to 10.0 mg produced effects of similar magnitude.

Daytime sleepiness, a common adverse reaction of melatonin when administered for jet lag, has been shown to be dose-dependent. Since the most common used methodologies to evaluate the effects of melatonin on prevention and treatment of jet lag and treatment of shift work disorder include self-rated Visual Analogue Scale (VAS), Profile of Mood States (POMS), actigraphy, sleep diaries and questionnaires, the correlation of concentration – time curves of melatonin and desired clinical effects is difficult. Most of the clinical studies evaluate the fatigue, the daytime tiredness, the onset of sleep at destination the onset and quality of sleep, the psychological functioning and the duration of return to normal. On the other hand, melatonin displays a high inter-individual variability in the parameter of serum levels and the correlation of different doses of melatonin with the clinical effect is therefore difficult. In a study, melatonin dosing induced dose-dependently decrements in alertness and performance efficiency. Moreover, 0.5 and 3.0 mg of melatonin induced the same magnitude of phase advance (~1 h), while the 3.0-dose caused sleepiness and performance decrement in the period between melatonin ingestion and bedtimes. In a study of 1 h sleep schedule advance combined with both early morning light and afternoon melatonin treatment (0.5 or 3 mg), it was demonstrated that the addition of melatonin caused a significantly greater phase advance of 2.5 h. Although there was no significant difference in phase shift between the 2 doses, a slight difference was noted in the sleepiness they produced. The 3.0 mg dose made subjects sleepier, whereas sleepiness after the 0.5 mg dose was almost identical to that observed after placebo.

Overall, it has been proved that even doses as low as 0.5 mg are sufficient to promote phase advances or phase delays, dependently on the time of administration and thus is effective for the prevention, treatment and/or alleviation of jet lag. High doses of melatonin (5-80 mg) are soporific, as melatonin mainly exerts its hypnotic effect. In general, many reviews and reports, based on subjective measures of jet lag suggested that melatonin is effective at doses of 2-5 mg taken shortly before bedtime. It was also shown that immediate formulations are more efficacious in the treatment of jet lag than controlled release formulations.

Doses that produce plasma levels over 200-400 pg/ml (produced with approximately 0.5-1.0 mg IR melatonin), are deemed efficient and safe, when the time of administration is the appropriate for the treatment of jet lag. Thus, low, IR administered shortly before bedtime in the new time zone are hypothesised from a PD point of view to be beneficial in alleviating perceived jet lag effects.

Glucose levels and on endogenous melatonin secretion
In regards to the effects of melatonin on glucose levels and the potential suppression of endogenous melatonin secretion during long-term therapy, identified studies generally suggest a beneficial role for melatonin on glucose metabolism, whereas exogenous melatonin supplementation is not found to suppress endogenous production even in long-term use.

QTc prolongation
An *in vivo* study in rats investigated the effects of melatonin on the regulation of the blood pressure and the relationships between the expressions of aorta KCNQ1-5, left ventricle KCNH2 genes and the QTc interval. KCNQ genes expressed in aorta are related with vascular tone and KCNH2 gene characterised in left ventricle are associated with QT duration. Melatonin was able to prevent QTc prolongations and decreases in KCNH2 gene expression level. These findings were further supported by a later *in vivo* study where a similar decreasing effect of melatonin on QT and QTc prolongation was demonstrated. On the contrary, melatonin did not modify QT interval duration in a porcine model of acute myocardial ischemia.

Pharmacodynamic interactions with other medicinal products or substances
Anaethetics: Melatonin premedication has been shown to significantly decrease the doses of both propofol and thiopental required to induce anaesthesia. In a prospective, randomised, double-blind study, 200 adults with ASA (American Society of Anaesthesiologists) physical status I received orally either 0.2 mg melatonin/kg or a placebo for premedication (n=100/group). After ~50 min, subgroups of 10 melatonin and 10 placebo patients were administered various doses of propofol (0.5, 1.0, 1.5, 2.0, or 2.4 mg/kg) or thiopental (2.0, 3.0, 4.0, 5.0, or 6.0 mg/kg) for anaesthetic induction. The results showed that melatonin premedication decreased thiopental median effective dose (ED_{50}) values for loss of response to verbal command and eyelash reflex from 3.4 mg/kg (95% CI, 3.2-3.5 mg/kg) and 3.7 mg/kg (3.5-3.9 mg/kg) to 2.7 mg/kg (2.6-2.9 mg/kg) and 2.6 mg/kg (2.5-2.7 mg/kg), respectively ($P<0.05$). Corresponding propofol ED_{50} values decreased from 1.5 mg/kg (1.4-1.6 mg/kg) and 1.6 mg/kg (1.5-1.7 mg/kg) to 0.9 mg/kg (0.8-0.96 mg/kg) and 0.9 mg/kg (0.8-0.95 mg/kg), respectively ($P<0.05$).

Atorvastatin: The efficacy of the combination of melatonin plus atorvastatin against endothelial cell damage induced by inflammation and oxidative stress injury has been investigated using human umbilical vein endothelial cells (HUVEC) cultured with bacterial lipopolysaccharide (LPS) in the presence or absence of melatonin and/or atorvastatin. LPS inhibited endothelial nitric oxide synthase (eNOS) mRNA and protein expression, which was reversed by atorvastatin and, to a lesser extent, by melatonin. Melatonin plus atorvastatin induced higher eNOS protein expression than either compound alone. Melatonin, but not atorvastatin, reduced free radical generation, lipid peroxidation, and IL-6 levels induced by LPS. In the presence of atorvastatin, the effects of melatonin were maintained or even improved. These data suggest that melatonin improves the beneficial effects of atorvastatin and reduces its AEs in endothelial cells during inflammation and under conditions of oxidative stress.

Carbamazepine: In a double-blind, randomised, parallel-group, placebo-controlled trial, in which 31 (seizure-free for ≥6 months) children with epilepsy receiving carbamazepine monotherapy were co-administered (add-on treatment) melatonin (6-9 mg/day for 14 days) or placebo, an increase in glutathione reductase (GRd) activity was noted in the melatonin group as compared with a decrease of the same enzyme in the placebo one. Changes in GPx activity failed to reach statistical significance. No significant changes were found in the serum levels of carbamazepine and carbamazepine-10,11-epoxide in either group.

Naloxone: Twelve healthy subjects (nen and women) were administered melatonin alone (0.4 mg/kg, intramuscularly, at 09:00 h) and on a separate occasion after a simultaneously with naloxone (1.2 mg IV bolus, followed by an IV infusion of 1.6 mg/h for 3 h). On another occasion, the study was performed during saline or naloxone infusion alone. A significant rise of growth hormone (GH) was observed after melatonin injection alone, whereas the simultaneous infusion of naloxone blocked melatonin-induced GH rise. Melatonin did not affect LH serum levels, while it was able to reduce LH increase induced by naloxone.

Olanzapine: There is promising evidence of the potential benefits of melatonin and its agonists in attenuating one or more components of metabolic syndrome among psychiatric patients using atypical antipsychotics. The effect of melatonin on metabolic AEs of olanzapine was evaluated in a randomised, double-blind, placebo-controlled trial of 48 patients with first episode schizophrenia who were eligible for olanzapine treatment. Patients were randomly assigned to olanzapine plus either melatonin 3 mg/day or matched placebo

and were followed for 8 weeks. Metabolic parameters including weight, waist circumference, triglycerides, cholesterol, insulin, and blood sugar were assessed at baseline, week 4 and 8. The study found that melatonin was associated with significantly less weight gain, increase in waist circumference and triglycerides than the placebo. Changes in cholesterol, insulin, and blood sugar did not differ significantly between the two groups.

Zolpidem: A randomised, double-blind, placebo-controlled, 4-way crossover study assessed the effects of therapeutic oral doses of prolonged-release melatonin (2 mg), zolpidem (10 mg) and their combination (given at bedtime) in cognitive functions in healthy subjects. A new PD interaction (potentiation of CNS effects) between melatonin and zolpidem at 1 h after co-administration was observed, which was partly attenuated by 4 h. Melatonin concentrations after administration of melatonin and melatonin+zolpidem were comparable with T_{max} of 1-2 h. The same scheme was also noted for zolpidem concentration; thus, a PK interaction can be discarded. Melatonin was not found associated with impairment of psychomotor functions, memory recall and driving skills and point to a PD interaction between melatonin and $GABA_A$ modulators.

Other CNS drugs: Concomitant administration of melatonin and drugs affect the CNS may result in PD drug interactions. For instance, relative to monotherapy with the CNS-active drug, patients receiving prolonged-release melatonin and imipramine had increased feelings of tranquillity and difficulty in performing tasks, and those receiving prolonged-release melatonin plus thioridazine had increased feelings of 'muzzy-headedness'. In a study in which Alzheimer's patients with sleep disturbances were treated with melatonin 3 mg capsules for 21 days, those who received 25 mg thioridazine daily interrupted thioridazine treatment after 5 and 24 months of melatonin treatment initiation due to behavioural and sleep disorders, respectively.

Quinolones: A study demonstrated that the antibacterial activity of ciprofloxacin was inhibited by pretreatment of bacteria with antioxidant agents such as melatonin. This interaction is likely to be related to the interference with induction of ROS by ciprofloxacin.

Alcohol: Alcohol should not be taken with melatonin because it reduces the effectiveness of melatonin on sleep.

Chemotherapeutic agents: Both melatonin and two tested chemotherapeutic agents, i.e., cisplatin and 5-FU, induced a decrease in human colorectal cancer HT-29 and cervical cancer HeLa cell viability. In addition, melatonin significantly increased the cytotoxic effect of chemotherapeutic agents, particularly, in 5-FU-challenged cells. Stimulation of cells with either of the two chemotherapeutic agents in the presence of melatonin further increased caspase-3 activation. Concomitant treatments with melatonin and chemotherapeutic agents augmented the population of apoptotic cells compared to chemotherapeutic monotherapies.

IV.4 Clinical efficacy

Jet lag is a syndrome associated with long-haul flights across several time zones, characterised by sleep disturbances, daytime fatigue, reduced performance, gastrointestinal (GI) problems, loss of mental efficiency, weakness and irritability, and generalised malaise. As with most syndromes, not all of the components must be present in any one case. Jet lag affects most air travellers crossing ≥5 times zones; the incidence and severity of jet lag increase with the number of time zones crossed. Westward travel causes less disruption than eastward travel as it is easier to lengthen, rather than to shorten, the natural circadian cycle. The sleep loss caused by the travel itself often contributes to jet lag. After a flight through ≥6

time zones most travellers will take 4-6 days to re-establish a normal sleeping pattern and not to feel tired during the day.

Melatonin's excretion from the pineal gland and its action on melanocytes has been known since its first *in vivo* isolation. However, most importantly it was identified that the first clinical studies evaluating the efficacy and safety of melatonin use in the treatment of jet-lag, as well as studies investigating its PKs have been published since the late 1980s. Melatonin efficacy aspects are also currently being reviewed as noticed in many review papers and meta-analyses of clinical trials identified.

Additionally, many published guidelines of medical organisations, associations and institutions promote the use of melatonin in the treatment of jet lag, namely the American Academy of Sleep Medicine (AASM), British Association for Psychopharmacology, Health Canada, Mayo Clinic, the International Federation of Sports Medicine and the US National Academy of Sciences.

A thorough screening of the literature has identified 26 clinical studies dealing with the use of melatonin in jet lag. Among them, 16 studies involving both eastwards and westwards travel concluded that melatonin is effective for the treatment of jet lag, 6 studies administered melatonin after inducing a phase shift, 2 studies concluded that melatonin is not effective for the treatment of jet lag, one study concluded that melatonin was effective only if its administration starts after travel and one study concluded that melatonin does not alleviate subjective jet lag but helps resynchronisation of cortisol levels when travelling eastwards.

Table 11. Clinical studies identified in the literature investigating the efficacy of melatonin in the treatment of jet lag

Study type	Doses	N	Time zones	Direction	Time of administration	Endpoints	Conclusion
Double-blind randomised placebo-controlled	5 mg	17	8	eastward	Pre-flight at 18:00h for 3 days and after flight at 22-24:00h local time for 4 days	Subjective VAS jet lag. Sleep quality Body temperature. Performance. Alertness. Depression. Endogenous melatonin and cortisol rhythms.	Melatonin significantly improved 'jet lag'
Double-blind crossover placebo-controlled	5 mg	52	8-9	eastward	Pre-flight at 17:00am for 2 days and after flight at 22-24:00 local time for 4 days (for phase advance)	Subjective VAS of jet lag. General symptoms of jet lag	Melatonin significantly improved 'jet lag'
				westward	Only after flight at 22-24:00 local time for 4 days (for phase delay)		
Double-blind crossover placebo-controlled study	5mg	61	9-11	eastward	Pre-flight at 18:00am for 2 days and after flight at 22-24:00 local time for 4 days (for phase advance)	Subjective VAS of jet lag. General symptoms of jet lag	Melatonin significantly improved 'jet lag'
				westward	Only after flight at 22-24:00 local time for 4 days (for phase delay)		
Double blind cross over placebo controlled	5mg	586	8-11	eastward	Pre-flight at 18:00am for 2 days and after flight at 22-24:00 local time for 4 days (for phase advance)	Subjective VAS of jet lag. General symptoms of jet lag	50% reduction of self- rated jet-lag.
				westward	Only after flight at 22-24:00 local time for 4 days (for phase delay)		

Coss over placebo controlled	5mg	36	6, 9 or 11	eastward	After flight at 23:00 local time of destination for 5 days, no pre-flight treatment	Subjective VAS of jet lag. Cortisol blood levels re-adaptation	Accelerated cortisol adaptation, non-significant VAS improvement
				westward			Not significant improvement compared to placebo
Double blind randomised placebo controlled	8mg	37	6-8	eastward	On flight day at 17-18:00 and after arrival at 22-23:00 local time for 3 days	Subjective VAS questionnaire on the global treatment efficiency, sleepiness., morning mood, fatigue, work performance	VAS of jet lag, sleepiness and sleep improved
Double blind placebo controlled	10mg	29	8	eastward	For 3 days preflight at 15:30-16:00 (pre-bed at destination time), on flight day 15:30-18:00h and after arrival 30min pre-bedtime for 4 days (for 8 hours phase advance)	Sleep duration, cognitive performance, activity rhythms were recorded contirnously for 13 days	Melatonin significnalty improved endpoints and helped resynchroniatio n.
Double-blind randomised placebo controlled study.	0.5mg IR, 5.0mg IR, 2.0mg CR	320	6-8	eastward	After flight once daily at bedtime for 4 days	Profile of Mood States (POMS), sleep log, Jet lag symptoms questionnaires, Karolinska Sleepiness Scale (KSS)	Melatonin improved jet lag. IR better than CR. Almost equal effects 0.5mg IR with 5.0mg IR.
Double-blind, randomised, placebo-controlled study	1)5 mg melatonin 2)10 mg zolpidem 3)5mg melatonin + 10mg zolpidem 4) placebo	137	6-9	eastward	After flight once daily at bedtime for 4 days	Daily sleep logs, Symptoms' questionnaires, Profile of Mood States (POMS), Subjective VAS for jet lag, Actigraphy	All 3 treatments led to a decrease of jet lag severity with zolpidem being the most effective treatment.
Double-blind placebo-controlled trial	5 mg	52	11-12	westward	1) **early melatonin group** (melatonin 3 days before arrival at destination and 5 days after-flight) 2) **late melatonin group** (placebo for 3 days bedore arrival at destination and melatonin for 5 days after flight) 3)**placebo group**	Subjective VAS for jet lag, Sleepiness, Fatigue, Vigour, Activity	Statistically significant improvement in the group receiving melatonin only after flight (late melatonin)
Double-blind, placebo-controlled crossover trial	5 mg	20	12	eastward	Pre-flight at 10-12:00 (local time) for 3 days, on flight day at 10-12:00 and for 3 days after flight at 22-24:00 (destination time).	Subjective VAS for jet lag, Sleepiness, Fatigue, Vigour, Activity, Daytime tiredness	VAS jet lag improved with melatonin compared to placebo
				westward			VAS jet lag was improved and sleep was re-established quicker with melatonin than placebo
Double-blind, randomised placebo-controlled trial.	1) 5.0 mg melatonin at bedtime (n=64). 2) 0.5mg melatonin at bed time (n=70). 3) 0.5mg melatonin on	257	6	eastward	Groups 1),2) and 4) on flight day and after flight at local bedtime for 5 days. Group 3) on flight day 11h after subjects's usual wake up time and for the next 5 days one hour	Columbia Jet Lag Scale	Melatonin had no effect in alleviating jet lag sympotms compared to placebo

	an advancing schedule (n=63) 4) placebo (n=60)				earlier every evening.		
Double-blind crossover design placebo-controlled. Jet lag simulation study inducing 9h phase advance in isolated facility	5mg	8	9	eastward (need to phase advance)	Pre-flight (before inducing phase shift) at 18:00h (local time) for 3 days and at 14:00h after-flight (after inducing phase shift) for 4 days	Body temperature. Urine excretion of: corticosteroids, calcium, potassium, sodium. Performance tests, Sleep daily logs Subjective questionnaire for jet lag. Stanford Sleepiness Scale.	Melatonin hasted resynchronizati on versus placebo of the majority of variables measured.
Double-blind, randomised, four-leg crossover; placebo-controlled study Jet lag simulation study in a controlled environment	1)5mg melatonin + dim light 2)placebo + dim light, 3)5mg melatonin + bright light 4)bright light + placebo	8	9	eastward (need to phase advance)	After flight (after inducing phase shift) at 23:00 for 3 days. Bright light at 0800-1200h for 2 days after phase shifting in groups 3) and 4)	Body temperature. Subjective behavioral measurements Urinary 6-Sulphatoxymelatoni n	Melatonin improved re-synchronisation of body temperature, sleep, alertness and performance efficiancy, irrespectively of light
Double-blind, randomised, placebo-controlled study with 3 groups	1)300mg SR caffeine 2)5mg melatonin 3)placebo	27 (9 per group)	7	eastward	Group 1) Caffeine was administered for 5 days after flight at 8:00 Group 2) Melatonin was administrered pre-flight at 17:00 on flight day at 16:00 and after arrival for 3 days at 23:00	Sleep, Daytime sleepiness, Oral temperature, Saliva melatonin, Saliva cortisol	Melatonin had beneficial effects on jet lag treatment mainly by improving sleep. Melatonin helped the resynchronisatio n of hormones
Placebo-controlled double-blind	5 mg	31	10	eastward	On flight day 18:00-19:00 (local time) and after-flight for 4 days at 22:00-23:00 (destination time)	Grip strength and intra-aural temperature, Subjective VAS of jet lag, Subjective questionnaire	Melatonin did not show any difference from placebo
Double blind, repeated measures, placebo controlled	3 transatlantic missions over which they took each of the 3 medications: placebo, 2mg melatonin SR, 7.5mg zopiclone	30	5	eastward	After arrival 17:00 body clock (22:00 local time) only once	Actigraphy, Sleep log diaries, Subjective questionnaire on sleep	Melatonin and Zopiclone improved sleep measures equally and both were better than placebo
All the same protocol of melatonin, light and exercise. There was no placebo control.	3 mg	22	12	westward	On flight day at 11:00 and after flight for 6 days at 23:00 (destination time)	Sleep log diaries, Subjective questionnaire on sleep, Morning alertness, Actogrms, urinary 6-Sulphatoxymelatoni n	Melatonin resynchronised sleep and wakefulness in an average of 2,13 days significantly different from the 6 days expected after a 12-h shift
All the same protocol of melatonin, light and exercise.	3 mg	75	13	eastward	On flight day melatonin at 10:00 (local time) after flight 30 min pre-bedtime for 7 days	Subjective VAS for jet lag, Sleep log diaries, Actogrms based on sleep log diaries,	Melatonin resynchronised sleep and wakefulness in an average of

There was no placebo control.							2,27 days faster than expected
		59	11	westward	Pre-flight for 7 days (as they were passengers form the eastward fligt) pre-bedtime on flight day at 13:00 (local time) and after flight 30min pre-bedtime for 8 days		Melatonin resynchronised sleep and wakefulness in an average of 2,54 days faster than expected after 13h phase shift
Within-subject placebo-controlled counter-balanced study	3mg	12	a gradual advance 1 h/day)	11 hours before baseline sleep midpoint on the first treatment day and 1 h earlier each subsequent day for 3 days		Dim Light Melatonin Onset (DLMO) from saliva, Sleep, Subjective symptoms rating, Psychomotor Vigilance and Subjective Sleepiness	Melatonin produced significantly larger phase advances (1.3 ± 0.7 h) compared to placebo (0.7 ± 0.7 h)
Double-blind placebo-controlled for melatonin.	0.5mg	50	1 hour per day phase shifting for 3 days	Melatonin 5h before baseline bedtime on treatment day1 and an hour earlier each day for 3 days. Subjects received three different morning bright light exposure patterns		Dim Light Melatonin Onset (DLMO) from saliva, Actigraphy, Subjective symptoms from Columbia Jet lag Scale and from Sanford Sleepiness Scale	Melatonin helped phase advance. The average magnitude of phase shift was equal to 3mg
No placebo group	5mg	14	6	eastward westward	After-flight at 23:00 (destination time) time during the flight and the first evening	Subjective questionnaire on sleep and wake-up quality compared to previous experiences of transcontinental travel.	Melatonin was found to effectively imporve symptoms of jet lag
Double blind placebo controlled, between-subjects design with melatonin dose as independent variable.	1) placebo (n=12) 2)0.5mg melatonin (n=9) 3)3.0mg melatonin (n=11)	32	7	eastward (need to phase advance)	After flight (after inducing the phase shift) 30 min before bedtime for 4 days	Body temperature, Dim light melatonin onset (DLMO) from saliva samples, Actigraphy, Subjective ratings of sleep, sleepiness and mood	Melatonin significantly helped to induce a phase advance and helped resyncrhonisation compared to placebo
Comparison with sampling 1 day prior and 1 day after melatonin administration (Takahashi et al., 2001)	3 mg	8	11	eastward	After-flight on the second day at 20:00 local time for 3 days	Subjective symptoms according to the Stanford Sleepiness Scale (SSS), Subjective VAS for jet lag, Blood levels of melaonin	Melatonin promoted antidomic re-entrainment, accelerated the rate of re-entrainment by 15 min per day and alleviated the jet lag symptoms
Comparison with sampling 1 day prior and 1 day after melatonin administration (Takahashi et al., 1999)	3 mg	6	8	eastward	After-flight on the second day at 23:00 local time for 3 days	Blood levels of melatonin	Melatonin significantly hastened re-synchronization. Re-entrainement without melatonin was 31min/day with melatonin 76 min/day.

Placebo-controlled, 4-week within-subject crossover design	5 mg	9	Phase shifts indu-ced by bright light, mela-tonin, their combina tion	Melatonin or placebo at 20:40 hr, with or without a subsequent 3 hr light pulse (5000 lux) from 21–24 hr.	Saliva melatonin levels. Dim light melatonin onset (DLMO)	Melatonin significantly induced a phase advance compared to placebo

After a first screening of the clinical studies identified, the main difficulties regarding the administration of melatonin in this indication reside in the posology, the dosing scheme, the duration of treatment and significant variability in jet lag related to the time zones changed, whether the travel is eastward or westward and other idiosyncratic characteristics. Another difficulty that this indication discloses is the lack of objective endpoints establishing its efficacy in a specific dose regimen for a specific period. The majority of studies used a subjective VAS of jet lag to assess its treatment. Other subjective endpoints commonly used were daytime sleepiness, alertness, depression, fatigue, performance in work or sports etc. Only few studies used objective measures such as wrist actigraphy, cortisol levels, melatonin levels, sleep characteristics (onset, latency, quality) and body temperature.

In order to elucidate these aspects, the applicant consulted several review papers, and performed an analysis of the data gathered, as presented below.

Review papers

A meta-analysis reviewing 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, concluded that melatonin does not have a significant clinical benefit. This may have been because the investigators mainly examined the effect of melatonin on sleep onset latency or sleep efficiency; however, the main mechanism of action of melatonin for jet lag is its action as a chronobiotic by helping resynchronisation of all circadian rhythms resulting in less daytime fatigue and ameliorating many aspects of all-day long routine.

It has been proposed that the administration of 5 mg melatonin for the treatment of jet lag in athletes, especially during daytime, does not provide any clinical benefit in relation to athletic performance and sleep. However, a Cochrane meta-analysis found that melatonin, taken close to the target bedtime at the destination (10 pm to midnight), decreased jet lag from flights crossing ≥5 time zones, by including 10 trials that met the inclusion criteria. Eight of the 10 trials found that melatonin, taken close to the target bedtime at the destination (10 pm to midnight), decreased jet-lag from flights crossing ≥5 time zones. Daily doses of melatonin between 0.5 and 5 mg are similarly effective, except that people fall asleep faster and sleep better after 5 mg than 0.5 mg. Doses above 5 mg 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. The reviewers 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 ≥5 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 required.

Another meta-analysis combined 11 randomised trials and generated a summary of findings following the GRADE approach. It has been concluded that the use of oral melatonin reduces the symptoms associated with jet lag syndrome.

A number of published review papers agree in the efficacy of 0.5-5.0 mg of melatonin in the treatment of jet lag in travellers. As already mentioned, the timing of administration is very important as receiving melatonin at times when it should be released naturally helps re-adaptation to the new time zone by resetting the body's biological clock to match the new environmental time and thus attenuates symptoms of jet lag. Therefore, a well-programmed schedule of melatonin intake and light exposure is suggested to be followed depending on the time zones crossed and the travel direction. For eastward travels, crossing ≤9 time zones, the proposed schedule included 3 days of pretreatment with melatonin at doses of 2-5mg at 14:00-18:00 local time, while phase advancing also sleep and wake cycle 1 h per day and controlling light exposure in the evening and after arrival 2-5mg at 22:00-24:00 bedtime destination, i.e., 30-60 min before bedtime for 3-5 days. For pre-adaptation delaying normal sleep, travellers are recommended to be exposed after arrival to daylight till the desired bedtime and receive 2-5 mg melatonin after arrival at 22:00-24:00 bedtime destination, i.e., 30-60 min before bedtime for 3-5 days. For both eastwards and westwards travels crossing >9 time zones, despite the fact that there is not an established scheme, the most cited included staying up later with exposure to bright light and receiving 1 mg non-soporific dose of melatonin on rising for one day, on flight day again 1 mg melatonin on rising and after arrival 2-5mg of melatonin at bedtime. In contrast, other reviews consider that there is no need for pretreatment with melatonin, as it practically does not provide any additional benefit. It is generally considered that, starting the administration on flight day or after arrival at destination 30-60 min before bedtime for 3-5 days is an effective scheme both for eastbound and westbound study irrespectively of the time zones crossed. For travels crossing <5 time zones, it seems that there is usually no need to receive any medication.

Basic Data Analysis of Clinical Studies presented in Table 11

As in many studies both eastward and westward travel were performed, resulting in different outcomes, every travel was considered as being a different occasion and evaluated separately. Thus, it was found that, in 21 evaluable studies (i.e., excluding those studies simulating jet lag by inducing phase shifts), 28 travels were performed.

Melatonin was proved beneficial in a total of 23 travels (15 eastwards and 8 westwards), found in a total of 17 studies. A total of 1,386 volunteers were included in these studies, of which 1,112 received melatonin and 437 received placebo. Doses used ranged from 0.5 mg to 10.0 mg with a mean(SD) value of 4.5(1.9) mg. On the other hand, melatonin was found ineffective in the treatment of jet-lag in a total of 5 travels (3 eastwards and 2 westwards), found in a total of 4 studies. A total of 348 volunteers were included in these studies, of which 260 received melatonin and 124 received placebo.

As evidenced by the studies evaluated, time of administration plays a crucial role for melatonin's effects on circadian rhythms. Administration time is strongly related to the desired effects. For instance, daytime administration of 0.1 to 0.3 mg generated serum melatonin C_{max} within the normal nocturnal ranges of untreated people. These and higher doses produce measurable hypnotic effects independently of the circadian time signal synchronising action. The need of a well-designed administration scheme is also supported by the fact that the observed differences on the effects of melatonin in relation to administration time, are not due to differences in PKs, but to differences in the already

existing melatonin concentration and in the phase of circadian human rhythm. Therefore, in order to find the optimum dosing scheme, an overall assessment of the studies identified was performed as described below.

Travels with pre-treatment
In 10 travels, administration of 0.5-5.0 mg melatonin (starting the administration pre-flight) showed a positive outcome. Among them, 7 travels were eastwards and 3 were westwards, with a change of 8-13 time zones. From a total of 661 volunteers, 520 received melatonin compared to 160 that received placebo.

In 2 travels, administration of >5 mg of melatonin (starting the administration pre-flight) showed a positive outcome. Both travels were eastwards with a change of 6-8 time zones. From a total of 66 volunteers, 36 received melatonin compared to 30 that received placebo.

In 3 travels, administration of 0.5-5.0 mg melatonin (starting the administration pre-flight) showed a negative outcome. Two of these travels were eastwards and one was westwards with a change of 6-11 time zones. From a total of 312 patients, 224 received melatonin compared to 88 that received placebo.

On the other hand, in a total of 13 travels (7 eastwards, 6 westwards), described within 11 studies found in the literature, melatonin was administered only after flight at 21:00-24:00 destination time for 3-5 days, in order to resynchronise sleep-time in the new time zone. Among these studies, in 11 travels (6 eastwards, 5 westwards) melatonin showed positive results, while in 2 travels (1 eastwards, 1 westwards) melatonin was ineffective.

Travels with treatment only after arrival
In 11 travels, administration of 0.5-5.0 mg melatonin (starting the administration after arrival at destination) showed a positive outcome. Among them, 6 travels were eastwards and 5 were westwards, with a change of 5-12 time zones. From a total of 772 volunteers, 555 received melatonin compared to 246 that received placebo.

In 0 travels, administration of >5mg melatonin (starting the administration after arrival) at destination showed a positive outcome.

In 2 travels, administration of 0.5-5.0 mg melatonin (starting the administration after arrival at destination) showed a negative outcome. The one travel was eastwards while the other was westwards with a change of 6-11 time zones. These two travels were part of the same double-blind placebo-controlled crossover trial where the 36 included volunteers were divided in two groups - one took melatonin eastwards and the other westwards.

Summary
In order to conclude, based on the clinical studies found in the literature, which is the most efficient scheme, the sum of the volunteers that underwent the one and the other treatment was considered:

- A total of 973 volunteers were included in studies where 0.5-5.0 mg melatonin or placebo was administered starting pre-flight. Among them, the 53% receiving melatonin showed a positive outcome while the 23% receiving melatonin showed a negative outcome.
- A total of 808 volunteers were included in studies where 0.5-5.0 mg melatonin or placebo was administered starting the administration after arrival at destination. Among them, the 69% receiving melatonin showed a positive outcome while the

4.5% receiving melatonin showed a negative outcome.

The percentage of volunteers that were effectively treated is higher in the studies where no pre-treatment took place. Also, the percentage of volunteers with a negative outcome shows a significant difference. Therefore, evidence shows that administration of 0.5-5.0 mg melatonin 30-60 min from bedtime after arrival at destination in the new time zone may be the most effective treatment with melatonin for jet lag. This is also supported by a study where from relevant comparison it was noticed that the group receiving melatonin only after flight showed alleviation from jet lag while the group receiving pre-flight melatonin showed a worse recovery compared to placebo.

This scheme and dosing is also in general agreement with the PKs of melatonin, suggesting a T_{max} at 30-50 min after administration; its PDs implying that melatonin receptors are saturated at levels above >200 pg/mL which is reached with a dose of >0.5 mg; the Melatonin monograph of Health Canada; and the SmPCs of the already marketed immediate release melatonin products in the EU with jet lag as an indication.

The fact that pre-treatment (administration pre-flight) with melatonin may not be necessary, is also in agreement with the SmPC of the IR melatonin products that are currently authorised in the EU with the indication of jet lag.

Efficacy studies simulating jet lag

In view of the wide variability of conditions under which clinical studies implementing travelling were performed, a careful assessment of studies evaluating the efficacy of melatonin after simulating jet lag disorder with induction of pre-defined phase shifts in volunteers, was also performed to gain deeper understanding of melatonin's chronobiotic effects.

A total of 6 studies investigating the efficacy of melatonin in inducing phase shifts towards a precise direction or in alleviating simulated jet lag in a controlled environment without the participation of volunteers in actual travels, were found and reviewed. The main advantage of these tests was the fact that the endpoints used were mainly objective, such as DLMO from saliva sample, urine excretion of hormones and electrolytes and sleep characteristics (onset, latency, quality), in combination with subjective measurements as subjective questionnaires on performance, fatigue, alertness and mood. Another advantage of these studies was also the possibility of completely controlling the exposure to light as a result, to assess only the effects of melatonin in resynchronization. However, these studies do not take into account normal travel fatigue, the average exposure to light during or after flight or other environmental factors but considers the effect only from the change of time zone.

All the studies proved that melatonin hastens resynchronisation and ameliorates jet lag symptoms. The doses of melatonin used were 0.5 mg, 3.0 mg or 5.0 mg and all of them exerted similar efficacy. Two out of 6 studies evaluated the effects of a gradual phase advance of 1 h/day induce with the help of melatonin 0.5 mg or 3.0 mg in healthy volunteers, 2 out of 6 studies started the administration of melatonin after the simulation of the travel, i.e. after inducing in volunteers 7-9 hours change of time zone in a controlled environment, one out of 6 studies started the administration of melatonin before the simulation of the travel, i.e. 3 days before inducing in volunteers 9 h change of time zone in a controlled environment, one study investigated the phase shifts that produced by 5 mg melatonin, with or without light exposure after administration in the late evening. In conclusion, also from these studies, the dosing scheme of 3.0-5.0 mg melatonin administered 30-60 min in the new time zone

seems to be effective.

Summary
Based on the above evaluated clinical data and on the numerous review papers, clinical guidelines and actual clinical use of melatonin as medicinal product or supplement, it may be concluded that the substance may present a clinical benefit in the treatment of jet lag as it hastens resynchronisation of circadian rhythms in the new time zones.

Although two of the reviewed studies were negative, the evidence is overall quite supportive that melatonin, administered at appropriate time, may reduce the symptoms of jet lag and improve sleep following travel across multiple time zones. Based on the published literature, efficacy of melatonin treatment for jet lag seems moderately convincing provided that a specified dosing schedule is followed, i.e., if it is taken close to the target bedtime at the destination; however, a harmonised approach regarding dosing recommendation is not achieved in the literature. IR formulations in doses of 0.5-5 mg appear effective. The vast variability of dosing schemes and doses proposed are noticed. The best clinical practice is not yet clear cut. In any case, it is suggested to prefer the administration of low doses of melatonin in order to both allow its chronobiotic effect to be manifested (even at 0.5 mg) and limit its hypnotic effect. This observation is in agreement with findings of studies related to PKs and PDs.

In the 2009 Cochrane Review, it is concluded that doses between 0.5 mg and 5 mg appear to be similarly effective, apart from the greater hypnotic effect of higher doses. For many people, 5 mg may be a higher dose than necessary: 2 or 3 mg may therefore be preferable to start with. It should also be noted that IR dosage forms are more efficient than sustained release for jet lag treatment.

Taking all the above studies and reviews into consideration, it may be concluded that the potentially best dosing scheme for eastward and maybe for westward flights, crossing more than 5 time zones, is 0.5-5.0 mg (most proposed: 2-3mg) of IR melatonin, 30-60min before bedtime at the destination time zone, starting on travel day and continuing for 3-5 days after arrival at destination until resynchronisation, based on subjective indices of jet lag. This scheme of dosing is also in general agreement with the PKs of melatonin and the SmPCs of the already marketed immediate release melatonin products in the EU/UK with jet lag as an indication.

Ten of the studies mentioned in Table 11 are also used in a 2002 Cochrane review of the effect of melatonin for the short-term treatment of jet-lag in adults using the main RCT in a meta-analysis. It is noted that differences are seen depending on whether travel was done eastward or westward.

The results are summarised below:

N = 17 (7M, 9P)	DB, PC Capsule	5mg 3d before & 4d after 8 time zones Eastwards	VAS (0-100) at day 7 ≥ 50 P: 6/9 (67%) M: 0/8*, mainly from decrease sleep latency
N= 10/10	DB, PC Crossover Capsule	5mg 3d before &3d after 12 time zones both directions	Number of days to normal sleep (SD): P = 4.15 (1.90) M = 2.85 (1.63) *
N= 15M/15P	DB, PC Capsule	8mg day of return + 3d after 6 time zones both directions	VAS (0-100) at day 8, median score: M=73, P=48P* Treatment efficiency (VAS ≥ 63):

			P= 5/15 (33%), M: 11/15 (73%)
Early/late/placebo N = 14/15/15	DB, PC Capsule	Early: 5mg 3d before & 5d after Late: 5d after 20 time zones	VAS at day 6, overall jet lag: Early= 66.7 Late= 37.7* Placebo= 64.7
N = 320 in 4 treatment groups	Randomised, DB, PC	0.5mg IR 5mg IR 2mg Slow release 4 d after 6-8 time zones east	5mg group better than other groups for sleep quality, latency, and duration.
N = 257 in 4 treatment groups	Randomised, DB Capsule	5mg at bedtime 0.5mg at bedtime 0.5mg shifting schedule 6 time zones east	No significant results in sleep or jet lag symptoms

*p<0.05; d = days; IR: immediate release; VAS: Visual Analog Scale; M= melatonin; P= placebo; DB: double-blind; PC: placebo-controlled.

Even though an improved performance of melatonin may be suggested for the eastward flights, this is mostly attributed to the higher likelihood of jet lag and its severity under these circumstances, however, this does not preclude the possibility of melatonin being beneficial for westward flights as well. For this reason, no specific reference regarding travel direction in the product information documents is deemed necessary.

Dose recommendations

Based on the extensive literature studies reviewed and evaluated, the optimal dosing scheme for eastward and potentially for westward flights, crossing more than 5 time zones, is 3.0-5.0 mg daily of IR melatonin, 30-60 min before bedtime at the destination time zone, starting on travel day and continuing for the consequent days after arrival at destination, until resynchronisation. For many people, 5 mg may be a higher dose than necessary, a 3 mg dose is considered as the standard starting point, but even a 6 mg daily dose might be needed if standard dose does not alleviate the symptoms. In any case, no safety issues are anticipated, given the PK profile but also the clinical safety data from published studies.

Also, available data do not actually support the initiation of melatonin prior to the day of the travel as it does not hasten or improve adaptation to local time at destination. Additionally, regarding duration of treatment, most studies provide data on efficacy up to 5 days, therefore this maximum is also proposed and present in other registered products' posology recommendations in case jet lag symptoms persist for so long. This treatment duration is supported by the published clinical studies, national clinical guidelines and justified by the expected clinical need, whereby most travellers will take approximately 4-6 days to re-establish a normal sleeping pattern and not to feel tired during the day.

Overall conclusions on Clinical Efficacy

The studies presented to support efficacy for the indication of short-term treatment of jet lag symptoms in adult patients are generally small, including 10-15 patients per arm, and three studies included around 60 subjects per arm. Most studies demonstrated statistically significant effects on jet lag symptoms or sleep.

Two of the studies conducted a responders analysis with respect to self-assessed jet lag severity and both showed a considerable difference (67% and 40%, respectively) in % responders. A study showed that melatonin treated subjects took on average one day less to return back to normal sleep (2.9 days compared to 4.2 days), which may be considered as clinically relevant.

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

Overall, it is considered that most studies demonstrated statistically significant effects on jet lag symptoms (e.g. mood, cognitive) or on sleep (which is perhaps the most important jet lag symptom) and that 2/10 studies with results for responders analysis concerning global jet lag symptoms of self-assessed jet lag severity demonstrated a considerable difference (67% and 40%, respectively) in percentage responders. In addition, a study showed that melatonin treated subjects took on average one day less to return back to normal sleep (2.9 days compared to 4.2 days), which may be considered as clinically relevant and as tapping into the ability to return back to normal functioning (i.e. work).

Of the 10 key jet-lag studies in the 2002 Cochrane Review, 7 investigated a dose of 5 mg once daily. One study noted some efficacy for the 0.5 mg and 5 mg doses but greater improvements in sleep onset latency and sleep quality for the higher dose, indicating a greater hypnotic effect. Another study suggested that a dose of 0.5 mg was not effective.

The effect of any stage of renal impairment on melatonin pharmacokinetics has not been studied. Caution should be used when melatonin is administered to such patients. Melatonin is not recommended for those with severe renal impairment.

There is no experience of the use of melatonin in patients with liver impairment. Published data demonstrates markedly elevated endogenous melatonin levels during daytime hours, due to decreased clearance in patients with hepatic impairment. Therefore, melatonin is not recommended for use in patients with hepatic impairment.

IV.5 Clinical safety

Melatonin-containing products for oral administration have been used within the EU and worldwide for many years. Thus, data relative to their safety result from clinical studies and from this extended post marketing experience. Up to date, no serious safety signals have been identified in clinical trials, nor any other pharmacovigilance alerts have been observed for oral melatonin products registered in EU/UK. A large literature search relative to the available publications in this field was made and the available data are presented below.

Adverse events

There is restricted published information regarding the potential adverse events (AEs) of (oral) melatonin administration. Melatonin is considered as being rather safe, as it is an endogenous substance that is well-tolerated even when administered at high doses (100 mg crystalline melatonin).

The most commonly reported adverse reactions of short-term melatonin use were nausea (incidence: ~1.5%), headache (incidence: ~7.8%), dizziness (incidence: 4.0%), and drowsiness (incidence: 20.3%); however, these effects were not significant compared to placebo. Melatonin treatment appeared to be well-tolerated in patients. This result did not change by dose, the presence or absence of a sleep disorder, type of sleep disorder, duration of treatment, gender, age, formulation of melatonin, use of concurrent medication, study design, quality score, and allocation concealment score. Melatonin doses below 8 mg have reportedly induced heavy head, headache, and transient depression. They may aggravate depression in patients with psychiatric illness as well. Some studies suggest melatonin may

deepen depression in those who have it or induce it in those susceptible to it. Fatigue occurs when melatonin is administered in the morning at higher doses (>50 mg).

Indeed, most studies involving melatonin dosing in humans point out that overall AEs of melatonin are insignificant and, in general, similar to those found with placebo. No hangover effects have been observed with melatonin when administered at reasonable concentrations, partially as a consequence of its short t½. However, high doses (240-1,000 mg/day) administered in a small number of subjects was associated with hormonal changes that were inconsistent among the different reports. Despite the lack of proper data, a meta-analysis that reviewed 10 controlled trials (over 200 subjects) with melatonin used for ≤ 3 months showed only scarce reports of AEs.

Suppression of endogenous melatonin secretion
Exogenous melatonin did not affect the production of endogenous melatonin in terms of secretion rate, amplitude and duration. A study measured the endogenous melatonin profiles after administration of a physiological dose of melatonin (0.5 mg) or placebo at bedtime to 21 night shift workers for seven days. The amplitude of endogenous melatonin secretion was unchanged by treatment. Additionally, a melatonin treatment trial using a 50-mg daily bedtime dose for 37 days to a blind subject resulted in no change in the endogenous melatonin profile.

A later study investigated the effects of an artificially prolonged melatonin (1.5 mg) profile on endogenous melatonin and cortisol rhythms, wrist actigraphy, and reproductive hormones in humans. Compared with placebo, melatonin administration advanced the timing of endogenous melatonin and cortisol rhythms. It was concluded that melatonin treatment did not affect the endogenous melatonin profile duration, pituitary/gonadal hormone levels (24 h), sleepiness and mood levels on the subsequent day.

Hepatotoxicity
In several clinical trials, melatonin was found to be well-tolerated and not associated with serum enzyme elevations or evidence of liver injury. Despite wide scale use, melatonin has not been convincingly linked to instances of clinically apparent liver injury. A review study provides a detailed and updated description of the protective effects of melatonin against various factor-induced liver injuries and diseases. Melatonin has shown protective effects in liver injuries induced by chemical pollutants, drugs, and alcohol, as well as liver diseases including hepatic steatosis, fatty liver, hepatitis, fibrosis, cirrhosis, and hepatocarcinoma. It could alleviate liver injuries and diseases by preventing oxidative damage, improving mitochondrial physiology, inhibiting liver neutrophil infiltration, necrosis, and apoptosis, reducing the severity of morphological alterations, and suppressing liver fibrosis. However, related studies of melatonin applied to clinical treatment for liver injuries and diseases are limited.

Cardiovascular system
AEs on blood pressure and heart rate in populations with cardiovascular conditions and concurrent antihypertensive medications have been reported with melatonin use. However, it is unclear whether these events are attributable to melatonin itself or to melatonin-drug interactions. The lack of information concerns also several other conditions, including autoimmune disorders, interactions with commonly used medicines etc.

The effect of 2 mg of melatonin or placebo on the Heart Rate Variability (HRV) of 26 healthy men was evaluated. Compared with placebo, melatonin administration within 60 min increased R-R interval, the square root of the mean of the squared differences between adjacent normal R-R intervals, high-frequency power, and low-frequency power of HRV and decreased the low-frequency to high-frequency ratio and blood pressure in the supine position (all, P<0.01). Plasma norepinephrine and dopamine levels in the supine position 60 min after melatonin administration were lower compared with placebo (P<0.05 and P<0.01, respectively). Standing up resulted in the decrease of HRV and the increase of blood pressure and plasma catecholamine levels in both administration groups, and the differences between the groups found in the supine position disappeared. Melatonin administration also may exert suppressive effects on sympathetic tone.

Glucose metabolism
Effects of melatonin on glucose metabolism have been shown and pathophysiology is known. Increased MTNR1B gene expression in risk allele carriers, might lead to a reduction in insulin release, increasing type 2 diabetes risk. It has also been discussed whether the variant in MTNR1B could predispose persons to glucose intolerance or type 2 diabetes under conditions of insulin resistance, such as obesity. Further studies concerning the possible role of exogenous melatonin in impaired glucose tolerance at this point are lacking.

CNS adverse reactions
A systematic review found one randomised controlled trial (RCT) demonstrating no significant difference between melatonin and placebo in AEs; another found that a disorientating 'rocking' feeling was significantly more frequent with melatonin (P=0.036). Hypnotic effects after melatonin occurred in 5 RCTs included in the review, affecting about 10% of people (further details not reported). Other effects included headache or heavy head (2 RCTs); disorientation (1 RCT); ear, nose, and throat problems; nausea; and GI problems (absolute numbers not reported; P values not reported). One person had difficulty in swallowing and breathing within 20 min after melatonin intake, but symptoms subsided after 45 min; they recurred after a further dose of melatonin. The review reported that the AEs in the trials occurred during treatment and seemed to have been short-lived. Six published and 19 unpublished case reports described possible related AEs on the CNS (including confusion, ataxia, headache, and convulsant effects), blood clotting (prothrombin increased or decreased, suspected interaction with warfarin), cardiovascular system (including chest pain and dyspnoea), and skin (fixed drug eruption). Although the review noted the difficulty of interpreting such data, it questioned the safety of melatonin in people with epilepsy and in people taking warfarin or other oral anticoagulants. It also suggested that people in these groups should not use melatonin without an informed (medical) discussion and concluded that further investigation was needed. In addition, the reports of fixed drug eruption, an allergic manifestation, appear to be convincing and must be taken seriously.

A recent comprehensive, critical systematic review of clinical evidence examined controlled studies of oral melatonin supplementation in humans when they presented any statistical analysis of AEs. Of the 50 articles identified, 26 found no statistically significant AEs while 24 articles reported on at least one statistically significant AE. AEs were generally minor, short-lived and easily managed, with the most commonly reported AEs relating to fatigue, mood, or psychomotor and neurocognitive performance. A few studies noted AEs 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 use in humans has a generally favourable safety profile with some exceptions. Most AEs can likely be easily avoided/managed by dosing according to natural circadian rhythms.

The indication of jet lag requires only low doses of melatonin for a short-term use (a few days). Therefore, the AEs encountered in clinical studies investigating the usefulness of melatonin for jet lag and its general toxicological and safety profile in order to cover the case of overdose, contraindications and interactions are presented below.

Safety outcome from clinical trials and authorised products with melatonin for jet lag
In a review which included 10 studies encompassing 487 participants, it was shown that melatonin is safe for short-term use; in particular, the most common melatonin-associated AEs were headache, dizziness, nausea and drowsiness and their incidence did not differ significantly with placebo. In a systematic review which analysed studies where melatonin (dose range: 0.5-10 mg, both IR and controlled-release formulations) was used to optimise sleep or improve sleep quality, no serious AEs or health risks from melatonin use were noted (n= 2,356 patients). However, the authors underlined that daytime administration of oral melatonin (0.1-1.0 mg) may cause drowsiness, fatigue and performance decrements, which appear to peak approximately 3-4 h after ingestion. A meta-analysis of data from RCTs involving individuals with delayed sleep phase disorder (DSPD) that compared melatonin (dose range in adults: 0.3-5 mg) with placebo concluded that the use of melatonin was safe with respect to experienced AEs at least in the short-term treatment (n=317).

In the studies reviewed, the most commonly reported AE was daytime sleepiness that can be limited by lowering the dose administered, without impairing the efficacy. The following Table summarises the AEs observed in RCTs involving melatonin administration for treatment of jet lag.

Table 12 Tabulated observations of AEs noticed in RCTs investigating the efficacy and safety of melatonin in the treatment of jet lag.

Melatonin dose	Number of subjects	Safety reports
5 mg	586 (474 melatonin, 112 placebo)	AEs reported more than once are (melatonin %-placebo %): sleepiness (8.3%-1.8%), headache (1.7%-2.7%), nausea (0.8%-0.9%), "fuzziness/giddiness" (0.6%-0%), and light-headedness (0.5%-0%).
0.5, 2.0 or 5.0 mg	234 (174 melatonin, 60 placebo)	The incidence of AEs had no difference between the 4 groups (placebo, 0.5 mg, 2.0 mg, 5.0 mg of melatonin). Most of the reported symptoms were the most common ones for jet lag, such as daytime sleepiness, headache, dizziness, or loss of appetite; these decreased with each treatment day and with equivalent incidence in melatonin- and placebo-treated groups
5 mg	137 (5 melatonin, 29 melatonin+ zolpidem, 39 placebo)	Combination melatonin/zolpidem were less well-tolerated than melatonin alone; AE reports included nausea, vomiting, amnesia and somnambulia to the point of incapacitation. Confusion, morning sleepiness and nausea were highest in the combination group
5 mg	26 (13 melatonin, 13 placebo)	A total of 6 subjects reported an increased number of headaches, 4 subjects reported dizziness and 6 subjects described a disorientating 'rocking' feeling. There was no significant difference between the melatonin and placebo groups for headaches and dizziness, but 5/6 subjects who reported a 'rocking' sensation were in the melatonin group.
5 mg	61 (crossover)	Infrequent AEs included drowsiness, headache, and nausea.
8 mg	37 (22 melatonin and 15 placebo)	Two cases of AEs were related to the hypnotic activity of melatonin. A single case of tachycardia and 2 cases of 'heavy head' were considered to be of minor consequence.
0.5 or 5.0 mg	257 (197 melatonin, 60 placebo)	There was no significant difference in the number of subjects, reporting AEs within the active treatment groups or within the placebo group. In one subject receiving 0.5 mg melatonin, difficulty swallowing, and breathing was reported almost 20 min after ingestion, symptoms that subsided after 45 min. Similar symptoms, although somewhat milder, did recur also in other volunteers.
5 mg	20 (crossover)	No AEs with either placebo or melatonin. Two subjects taking melatonin reported a mild sedative effect lasting about 0.5 h, and one other reported feeling more relaxed. Among subjects taking placebo, one reported increased tiredness, one a greater feeling of relaxation, and one a greater depth of sleep,
5 mg	44 (29 melatonin, 15 placebo)	5 of the 18 volunteers receiving pre-flight melatonin reported minor AEs. Two had sleeping difficulties after beginning the capsules, 1 felt drowsy for a brief time after taking melatonin, 1 complained of occasional headaches, and another felt depressed for 1 day after returning home. None of the subjects in the group receiving melatonin only after arrival or placebo reported AEs from taking the capsules 10 days.

Acute toxicity (short-term use)

In general, the most common AEs due to melatonin use in therapeutic dosages include sedation, drowsiness and mild hypothermia, altered sleep patterns, increased seizure activity in neurologically impaired paediatric patients, fatigue, headache, confusion, pruritus, and dysphoria. It is important to note that pre-existing medical or psychological conditions may contribute to the AEs. Specifically, concern of harm exists for individuals with one or more of the following: past or current depression, cardiovascular problems, seizure disorders, immune system disorders, chronic liver or renal disease, predisposition to headaches (especially migraine headaches) and concurrent use of anticonvulsant, sedative, hypnotic, or psychotropic medications.

Acute administration of melatonin appears to have little consistent effect on hormone levels in adult humans. Several early studies indicated effects of melatonin on GH secretion in men, whereas a comprehensive study has indicated that the only acute effect of melatonin was an elevation in prolactin levels, as determined in 24 young healthy males after oral

administration of 240 mg melatonin. Melatonin received in sufficiently high doses may also enhance GH levels, whereas various other hormones are not influenced.

Chronic toxicity

The absence of detectable gross toxicity after several months of melatonin administration does not rule out significant AEs. Some effects of melatonin administration may become apparent only after long latencies. A relevant example is the development of osteoporosis, which occurs earlier, more frequently, and to a greater extent in women with premature removal of the ovaries (or premature menopause) than in controls.

Correlation between a developmental decline in melatonin levels with the timing of puberty in humans led to speculation that melatonin regulates the timing of puberty. Subsequent investigation indicated that this developmental decline in melatonin levels is due at least in part to developmental changes in body mass (and thus, Vd) and is without a strict relationship to pubertal development. Although endogenous melatonin does not appear to play a role in timing human puberty, no data are available to draw a conclusion with respect to the effects of exogenous melatonin on puberty in humans. These data indicate that the amplitude of nocturnal melatonin secretion does not have a role in the regulation of reproductive events in menstrual primates.

The proposed indication for the melatonin product formulation under submission is for short-term administration to treat cases of jet lag. Therefore, there is no effect on endogenous melatonin secretion. There are published studies confirming the safety of melatonin use, even in long-term administration cases, with no effect on endogenous melatonin secretion having been observed. As mentioned above, chronic administration of melatonin appears to be well-tolerated. Women taking melatonin as a contraceptive agent ingest up to 300 mg/day; the initial report of this regimen indicated that no toxic effects were noted in the 4-month treatment period. Alterations in hormone concentrations noted in this study are viewed as evidence of melatonin's efficacy rather than as an indication of toxicity. Other examples of chronic melatonin treatment at lower doses (e.g., 5 mg/day for hypnotic effect) have been reported without obvious evidence of AEs; however abnormally high (or pharmacologic) concentrations of melatonin in women are associated with altered ovarian function and anovulation.

A limitation of a maximum of 16 treatment periods per year has been generally considered for melatonin treatment, as also included in several melatonin medicinal products' SmPC recommendations. This limits the theoretical continuous exposure to 80 days, corresponding to approximately 3 months, which is considered reasonable taking into account that large clinical studies and meta-analyses pooling data from melatonin trials performed in primary and secondary sleeping disorders, are mostly limited to treatment durations of 3-month periods, where melatonin was found to be in general safe. Final conclusions concerning further long-term safety of melatonin are limited by a general lack of randomised, 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. Nevertheless, as previously discussed, due to the limited knowledge on long-term effects of melatonin for example on endocrinology, it is considered important that there is a threshold of maximum exposure per year which is set sufficiently low, as is the case with the currently proposed maximum duration of 16 treatment periods per year.

From the above presented safety data, it is concluded that melatonin doses of 0.5-5.0 mg can be used safely in healthy adults for short-term treatment of jet lag based on literature data,

reports, reviews and clinical experience with already marketed products.

Pregnancy and lactation

Fertility and reproduction

Infertility treatments are associated with significant levels of reactive oxygen species which have the potential to negatively affect the quality of oocytes and embryos. Melatonin shows promise as an adjunctive therapy in the treatment of infertility due to its unique antioxidative characteristics and safety profile. Melatonin is also a key factor in the regulation of seasonal variation in gonadal activity. The circadian disturbances related to reproduction are probably subsequent to the seasonal change. Moreover, melatonin might also be considered essential for both spermatogenesis and folliculogenesis. Exposure to bright light, suppressing the concentration of melatonin in circulation, is considered to be useful in treatment of both male and female infertility in couples with abnormal melatonin metabolism.

Male reproductive toxicity: Constant short photoperiod causes gonadal arrest and reduction in the transcriptional activity of the cAMP responsive element modulator (CREM) gene in hamsters. Restoration of long photoperiod results in recovery of spermatogenesis. This modulation is dependent on the photoperiod, associated with the change in melatonin production, and can be reproduced by artificial lighting. Melatonin may be involved in the regulation of spermatogenesis or oogenesis during development and act as the hormonal messenger whose function would be to connect germ cells and Sertoli or follicular cells, respectively. Melatonin is a molecule with multiple properties (also, antioxidant and anti-apoptotic properties) that can also contribute to the improvement of male reproductive health and potential (particularly extrapineally produced melatonin). It can afford a protective effect not only in the treatment of many disorders that are known to have a deleterious impact on the male reproductive function (namely in diabetes mellitus, hyperlipidaemia, obesity, testicular torsion), but also against the effects of exogenous toxic agents. Melatonin seems to be capable to protect against several kinds of testicular injuries mainly through its antioxidant capacities.

Female reproductive toxicity: Bright light can regularise the length of the menstrual cycle in women with menstrual irregularity and possibly influence the time of ovulation. Several animal studies have shown that intrauterine metabolic programming can be modified in the event of reduced melatonin synthesis during pregnancy, leading to glucose intolerance and insulin resistance in the offspring. It is, therefore, postulated that female night workers when pregnant may expose the offspring to unwanted health threats which may be explained by the fact that melatonin is essential for regulating energy metabolism and can influence reproductive activity. Moreover, the circadian misalignment caused by shift work affects fertility and the foetus, increasing the risk of miscarriage, premature birth and low birth weight, phenomena observed in night workers. Melatonin is also considered to delay the ovarian aging due to its cytoprotective actions as an antioxidant. Indeed, in both animal models and women, melatonin supplementation suggests a therapeutic and preventative potential, effects attributed mainly to its antioxidant properties and action as hormone modulator.

A study observed that intrafollicular concentrations of melatonin were blunted in women with unexplained infertility, which was associated with a marked oxidative imbalance in the follicular fluid of such patients. Based on these findings, they performed a randomised pilot study to assess whether exogenous melatonin could ameliorate oxidative stress and improve in vitro fertilisation (IVF) success rates in unexplained infertility. Thus, 3 or 6 mg of melatonin/day were given to patients with unexplained infertility for a period spanning from

the first appointment to control ovarian stimulation until the day of follicular puncture. The results indicated that melatonin supplementation, irrespective of the doses tested, ameliorated intrafollicular oxidative balance and oocyte quality in the patients, and that this translated into a slight increase in the rate of pregnancies/live births. Therefore, although the melatonin has shown therapeutic potential in this clinical setting, larger clinical trials in populations with different backgrounds are encouraged to corroborate the usefulness of the hormone. Melatonin-containing supplements are easily found in online and high street retailers, and despite its supplementation deemed to be relatively safe, no consensus has been reached on effective dosage and supplementation period. Short-term supplementation studies, of up to 6 months, suggest that a daily posology of 2-18 mg of melatonin may have the potential to improve fertility rate, oocyte quality, maturation and number of embryos. However, the evidence available so far on the effects of melatonin supplementation covering gestational age and gestational outcomes is very scarce. Clinical trials and longer-term supplementation studies are required to assess any clinical outcome associated with melatonin supplementation in the field of gynaecology.

An early study has presented some data related to the influence of melatonin or melatonin-progestin combinations on the pituitary-ovarian axis and ovulation in 32 women. Melatonin was administered in a dosage of 300 mg to 12 women for 4 months, particularly, to 8 women daily (days 1-30) and to 4 women on days 5-17 of the cycle. A combination of melatonin plus the synthetic progestin norethisterone (NET) was given to 16 women, on days 1-21, at melatonin/NET dosages of 300/0.75 mg, 75/0.75 mg, 7.5/0.75 mg, and 75/0.30 mg. In addition, 2 women were medicated with 300 mg melatonin alone, and 2 were medicated with 300/0.15 mg NE on days 1-21 for 2 months. After 4 months, daily administration of 300 mg melatonin (days 1-30) caused significantly decreased mean luteinising hormone (LH) levels compared to those in 8 non-treated controls ($P<0.001$). Also, compared to the control data, a significant inhibition of progesterone in the 1st and 4th medication months ($P<0.001$) was observed. LH and E2 inhibition reached significance in the 4th month of treatment ($P<0.005$). Also, the treatments of 300 mg melatonin (days 5-17) and 75 mg melatonin combined with 0.3 mg NET caused a significant decrease in LH, E2, and progesterone levels compared to those in the control group in the 1st and 4th months ($P<0.05$). The data further suggest an additive or synergistic effect between melatonin and NET. The medications did not alter sleep-wake rhythms and were not complicated by any AEs.

According to the SmPCs of the marketed melatonin oral products, melatonin is not recommended in women and men planning pregnancy.

Pregnancy

The role of melatonin in embryofoetal development has been recently reviewed. The pineal gland develops completely postpartum, so both the embryo and the foetus are dependent on the maternal melatonin provided transplacentally. Melatonin appears to be involved in the normal outcome of pregnancy beginning with the oocyte quality and finishing with the parturition. Its pregnancy nighttime concentrations increase after 24 weeks of gestation, with significantly high levels after 32 weeks. MTs are widespread in the embryo and foetus since early stages. There is solid evidence that melatonin is neuroprotective and has a positive effect on the outcome of the compromised pregnancies. In addition, chronodisruption leads to a reproductive dysfunction and appears to be a key contributor to offspring diseases that develop in adult life (the concept of foetal programming). Melatonin decreases in conditions associated with serious outcome for the foetus and seems to be involved in pre-eclampsia and intrauterine growth restriction. Indeed, it has been suggested that exogenous melatonin increases glutathione peroxidase (GPx) activity in the chorion and thereby may protect

indirectly against free radical injury and thus it could be useful in treating pre-eclampsia and possibly other clinical states involving excessive free radical production, such as intrauterine foetal growth retardation and foetal hypoxia. Melatonin treatment during human normal or abnormal pregnancy has been studied for a large range of conditions and at different times during the gestational period. Considering the ethical issues, it is more difficult to study a normally occurring pregnancy, than an IVF one. Melatonin administration started prior to IVF-cycles, continued during pregnancy and was associated with improved pregnancy outcomes. MTs are widespread in the human fetus from early fetal development. In addition, it appears that the fetuses' sleep patterns develop in the late pregnancy, melatonin being the regulating factor. A normal sleep pattern is involved in the neurodevelopment and there is solid evidence that melatonin is involved in foetal neuroprotection. Thus, the influence of melatonin on the developing human foetus may not be limited to entertaining the circadian rhythmicity. Alterations in maternal or placental melatonin might alter foetal melatonin levels and thus, gene expression in the foetal nervous system.

Melatonin crosses the placenta in both humans and goats. Therefore, it is highly likely, if taken by pregnant women, that the foetus will be exposed to excess melatonin, and the possibility exists that it will modify subsequent development in terms of the circadian system and the timing of puberty.

According to SmPCs of the marketed melatonin oral products, melatonin is not recommended during pregnancy or in women of childbearing potential not using contraception.

Lactation and breastfed infants

Melatonin is a normal component of breast milk, with concentrations higher during nighttime (with a peak around 3 am) than daytime. Elective caesarean section results in higher daytime colostrum levels than with vaginal delivery. Some authors suggest that mothers should nurse in the dark at night in order to avoid reductions in the melatonin content of breast milk, which could disturb infant sleep patterns. Differentiating milk pumped during the day from milk pumped during darkness has also been suggested for women pumping milk for their infants. Some studies have attributed longer sleep time in breastfed infant than in formula-fed infants to melatonin in breast milk. Another study found higher colostrum melatonin levels at night which appeared to increase the phagocytic activity of colostral cells against bacteria.

Exogenous administration of melatonin has no specific use during breastfeeding; no data exist on the safety of maternal use of melatonin during breastfeeding. However, doses higher than those expected in breastmilk after maternal supplementation have been used safely in infants. It is unlikely that short-term use of usual doses of melatonin in the evening by a nursing mother would adversely affect her breastfed infant, although some authors recommend against its use in breastfeeding because of the lack of data and a relatively long t½ in preterm neonates.

As mentioned, melatonin exhibits a circadian rhythm in body fluids. No data are available on melatonin in human milk. A study determined whether melatonin is detectable in human milk and, if so, whether it exhibits a daily rhythm. Blood and milk were sampled between 14:00-17:00 h and again between 02:00-04:00 h from 10 mothers 3-4 days after delivery. Melatonin in both fluids was beyond the limit of detection during the day, whereas during the night, its concentration was 280±34 pmol/L in serum and 99±26 pmol/L in milk. Six mothers collected milk after each feeding throughout 1 24-h period within 3 months after delivery. Melatonin in the milk of all subjects exhibited a pronounced daily rhythm, with high levels during the

night and undetectable levels during the day. The presence of the rhythm in milk suggests that melatonin fluctuations in milk might communicate time of day information to breastfed infants.

An 18-month-old breastfed infant was having bleeding episodes since birth. A platelet aggregation test showed that the infant had reduced platelet aggregation after breastfeeding. When the infant was fasting, platelet aggregation was normal. The infant's mother was occasionally taking melatonin (dose not stated) for sleep. After she stopped melatonin intake for 3 months, the infant's platelet aggregation was normal and the infant had no further bleeding episodes, which were possibly caused by melatonin.

Adverse reactions
Drowsiness/sleepiness, headache, and dizziness/disorientation are the most frequently reported AEs of melatonin dosing on a short-term basis to treat jet-lag. Drowsiness, headache, dizziness, and nausea are also the adverse reactions reported most frequently when typical clinical doses of melatonin have been received for periods of several days to several weeks by healthy persons and patients.

The adverse reactions to melatonin reported in clinical trials or spontaneous case reports are described in Section 4.8 of the SmPC.

Melatonin has a moderate influence on the ability to drive and use machines. However, due to the increased subjective sleepiness after administration of this hormone, and as it may cause drowsiness and decrease alertness for several hours, its use is not recommended prior to driving and using machines.

Overall conclusions on clinical safety
The published safety information available for melatonin is limited. However, it is understood that there is extensive post marketing experience.

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.

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 a marketing authorisation is recommended for this application.

V USER CONSULTATION
A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product 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 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

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**