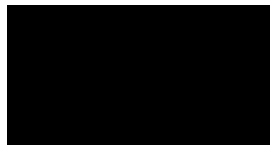


Melatonin 3 mg film-coated tablets

Module 2.5 - Clinical Overview

Applicant: Pharma Nord ApS



DENMARK

Date: 15 March 2023



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Abbreviations (key terms)

ACTH	adrenocorticotrophic hormone
ADHD	Attention Deficit Hyperactivity Disorder
ASMF	Active Substance Master File
AUC	area-under-the- (concentration-time) curve
BNF	British National Formulary
CBT	core body temperature
C _{max}	maximum concentration
CNS	central nervous system
CRSD	circadian rhythm sleep disorder
CSF	cerebrospinal fluid
CYP	cytochrome P450 system
DLMO	dim light melatonin onset
DSPD	Delayed Sleep Phase Disorder
EEG	electroencephalography
EFSA	European Food Safety Authority
EM(E)A	European Medicine Agency
FSH	follicle stimulating hormone
GABA	gamma-aminobutyric acid
GnRH	gonadotrophin-releasing hormone
HRT	hormone-replacement therapy
IR	immediate release
ITT	intention-to-treat (analysis)
<i>i.v.</i>	intravenous(ly)
IVF	<i>in vitro</i> fertilization (treatment)
LH	luteinising hormone
MAH	Marketing Authorisation Holder
MT1, MT2	melatonin receptors MT1 and MT2
OC	oral contraceptive(s)
OGGT	oral glucose tolerance test
PGI	potentially genotoxic impurity
PIL	Patient Information Leaflet
PSUR	Period Safety Update Report
RA	rheumatoid arthritis
RCT	randomised, controlled trial (placebo-controlled unless stated otherwise)
REM	rapid eye movement
RMP	Risk Management Plan
<i>s.c.</i>	subcutaneous(ly)
SCN	suprachiasmatic nucleus
SD	standard deviation
SE	standard error (of the mean)
SmPC	Summary of Product Characteristics
SOL	sleep onset latency
SWSD	Shift-Work Sleep Disorder
T _½	elimination half life
T _{max}	time to maximum concentration

TSH	thyroid stimulating hormone
TST	total sleep time
VAS	visual analog scale
WBC	white blood cells

CLINICAL OVERVIEW

2.5.1 PRODUCT DEVELOPMENT RATIONALE

Melatonin 3 mg film-coated tablets is an immediate release (IR) formulation containing 3 mg melatonin as the active substance. [REDACTED]

[REDACTED] data demonstrating that IR melatonin is effective for the treatment of jet-lag.

Melatonin is a hormone produced by the body. It has a number of functions but arguably the most important is its role in regulation of circadian rhythms, notably the sleep-wake cycle. Accumulation of knowledge regarding the role of endogenous melatonin in regulation of circadian rhythms, and identification of conditions in which the circadian rhythmicity of melatonin production is disturbed or not synchronised with day-night (e.g. in Delayed Sleep Phase Disorder (DSPD) and blind people with free-running circadian rhythm) have led to appropriately-timed administration of melatonin being tested as a treatment for circadian rhythm sleep disorders. Due to its capacity to induce sleep and improve overall sleep, melatonin has also been tested for sleep disorders in which the timing or amplitude of endogenous melatonin excretion is not necessarily impaired or confirmed impaired in an individual (e.g. insomnia, Attention Deficit Hyperactivity Disorder (ADHD), and sleep problems in people (particularly children and adolescents) with a neurodevelopmental disorder.

Melatonin has also been tested as a treatment for more transient, though often more extensive, circadian rhythm disturbances in which voluntary human activity desynchronises endogenous melatonin synthesis profile and the sleep-wake cycle. Such activities include shift-work, which can result in Shift-Work Sleep Disorder (SWSD), and rapid (air) travel across multiple time zones which can result in Jet-Lag Disorder (JLD) (generally referred to as jet-lag).

[REDACTED]

The efficacy and safety of melatonin in jet-lag has been demonstrated in placebo-controlled, randomised trials, [REDACTED] *Melatonin for the prevention and treatment of jet-lag* [REDACTED]. Additional studies document the capacity of exogenous melatonin to shift the timing, or to enhance the re-entrainment, of endogenous melatonin synthesis, and an extensive literature documents a good general safety profile of typical therapeutic doses of oral melatonin, even when administered daily for several months.

Several guidelines and expert recommendations, [REDACTED] support use of melatonin for treatment of [REDACTED]

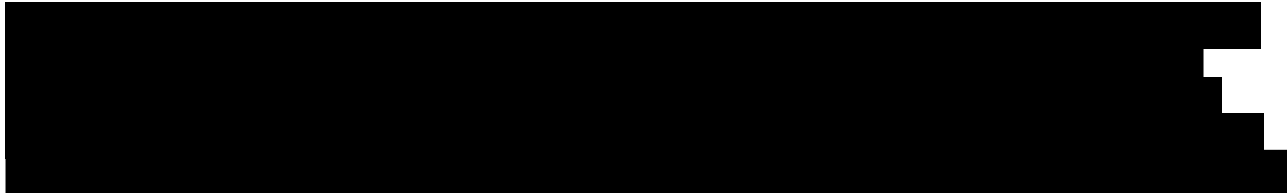
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This Marketing Authorisation is pursuant to Article 10a of Directive 2001/83/EC as amended (European Commission, Enterprise Directorate-General, Consumer goods, Pharmaceuticals. Notice to Applicants, Volume 2A. Procedures for marketing authorisation. Chapter 1. Marketing Authorisation. Revision 5, July 2015), relating to applications relying on well-established medicinal use supported by bibliographic literature.



Please note that this clinical overview concerns the subjects of melatonin in general and



2.5.2 OVERVIEW OF BIOPHARMACEUTICS

According to the Product Fact Sheet, Pharma Nord ApS, Denmark, produces Melatonin 3 mg film-coated tablets containing the ingredients listed in Table 2.5.2-1.

Table 2.5.2-1 Composition of Melatonin 3 mg film-coated tablets

Composition	
Melatonin	
Microcrystallose	
Microcrystallose	
Silica colloidal, anhydrous	
Hypromellose	
Carmellose Sodium	
Maltodextrin	
Magnesium stearate	

No pharmacokinetic studies have been made with the product Melatonin 3 mg film-coated tablets, however bioequivalence studies comparing the product with products considered representative of the interventions used in the relevant literature studies have been performed according to the appropriate guidelines (see [Section 3.2.P.2.2 Drug Product](#) for details).

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

2.5.3.1 Pharmacokinetics

No formal pharmacokinetic (PK) studies have been made with the Applicant's product. The PK data presented in this dossier are derived from published reports, primarily of studies in which the formulation(s) used (immediate-release¹ tablets or capsules with strengths up to 6 mg, taken orally) are considered relevant to the Applicant's product² and its posology (3 or 6 mg once daily). Not all the study reports specifically stated that the formulation(s) used were immediate release (IR), however this could generally be confirmed from reported Tmax values and/or the shape of plasma melatonin concentration-time curves.

Comparison of PK data for exogenous melatonin across studies – particularly studies with different designs and analytical methods – should be done with caution. As peak plasma melatonin concentration (Cmax) following oral administration shows large inter-individual variability, caution should also be applied when comparing data only available for a small number of subjects. When comparing the PK of exogenous- and endogenous melatonin, it should be noted that endogenous melatonin shows circadian rhythmicity and, like exogenous melatonin, considerable inter-individual variability in peak level (Cmax), which typically occurs between 02:00 – 04:00 hr [REDACTED] AUC⁴. Thus the optimal data for comparison of the PK of a melatonin formulation such as the Applicant's with the PK of endogenous melatonin would be collected from the same group of subjects following ingestion of 3 – 6 mg doses of IR melatonin at bedtime (22:00 – 24:00 hr)⁵. Such data are not available, however quite extensive published data allow reliable estimation of Cmax, AUC, Tmax, and T_{1/2}⁶ following ingestion of 3 – 6 mg IR melatonin, and comparison of these values to those for endogenous melatonin in the general population. The PK of melatonin has been summarised in a number of articles and official assessments, including the recent systematic review of the clinical PK of melatonin by [REDACTED]

2.5.3.1.1 Absorption

The physicochemical characteristics of melatonin (low molecular mass (232.3), logP (experimental) of 1.6, no physiological charge, hydrogen donor count 2 and hydrogen acceptor count 2) suggest rapid, efficient absorption [REDACTED]

2.5.3.1.1.1 Tmax

Five intervention studies described in more detail in [Section 2.5.3.1.1.2 Cmax](#) in which immediate-release melatonin was administered to healthy men and/or women reported mean plasma / serum Tmax values for dose in the range 3 – 6 mg of ~ 25 minutes

1 An alternative term is conventional release.

2 [REDACTED]

3 The evening onset of melatonin secretion and the peak level were ~ 1.5 – 2 h later in younger adults (20 – 43 years) compared to older adults (49 – 73 years).

4 Area under the concentration-time curve, which intergrates total plasma quantity in a given period.

5 The recommended time of intake of the Applicant's product as stated in the proposed SmPC.

6 Tmax = time at peak concentration; T_{1/2} = elimination half-life in serum / plasma.

~ 60 minutes ~ 50 minutes
 , 60 minutes and 40 minutes A sixth study (reported mean Tmax values of 40 and 53 minutes, respectively in 10 younger women and 8 older women following ingestion 6 mg IR melatonin. The data from the above 6 studies give an unweighted mean and median plasma / serum Tmax for exogenous melatonin of 45 minutes and 50 minutes, respectively. A systematic review of the clinical PK of melatonin (reported a Tmax of ~ 50 minutes for IR melatonin products (capsules and tablets). A RCT in which 2 groups of 8 young men ingested 5 mg melatonin (IR) at 13:00 hr or 18:00 hr found salivary melatonin Tmax to be earlier (30 minutes vs. ~ 65 minutes) and Cmax to be ~ double after intake at the earlier time of day, though it should be noted that the 2 experiments had different participants.

In summary, the above data indicates that 3 – 6 mg oral dose of immediate-release melatonin can be expected to have a Tmax of ~ 50 minutes. Tmax is essentially constant with typical therapeutic doses of melatonin. The implications of the brief Tmax for use of IR melatonin for treatment of jet-lag are considered under the heading *Timing of daily intake during the treatment period* in **Section 2.5.4.1.2 Efficacy findings and their implications** (Efficacy).

2.5.3.1.1.2 Cmax

Plasma or serum Cmax for 3 mg IR melatonin have been reported in a number of studies. reported a mean ($\pm$ SD) serum Cmax of 3561 ± 1201 pg/mL following ingestion of 3 mg melatonin⁷ at 09:30 hr by 7 healthy men (mean age 31 years). A mean serum Cmax of ~ 750 pg/mL for 6 healthy men (mean age 22.5 years) following ingestion of 3 mg melatonin (gelatine capsule with lactose) at 09:30 hr can be estimated from Figure 2b of the study report of . A plasma Cmax of ~ 3460 pg/mL can be estimated⁸ for a 3 mg dose of melatonin (capsule with sucrose) administered at 16:00 hr to 32 healthy men and women aged (18 – 38 years) (). A serum Cmax of ~ 3970 pg/mL can be estimated for a 3 mg dose of melatonin (tablet) administered between 07:00 – 09:00 hr to 12 healthy men and women (mean age 37 years) reported a mean ($\pm$ SD) plasma Cmax of 2405 ± 279 pg/mL for 3 mg melatonin (powder) administered at an unstated time to 20 healthy men and women (20 – 37 years), and reported a mean serum Cmax of 11,040 pg/mL following administration of 3 mg melatonin (crushed tablet) to critically ill patients. None of the above studies determined Cmax for endogenous melatonin. Excluding the value of ~ 750 pg/mL which seems uncharacteristically low, and the value of 11,040 pg/mL which is for critically ill patients, gives an unweighted mean and median plasma / serum Cmax of 3350 pg/mL and 3510 pg/mL, respectively, for a 3 mg dose of IR melatonin based on data from 4 studies.

The size of the above increase can be compared to Cmax for endogenous melatonin using data from a number of studies. reported a mean ($\pm$ SD) plasma Cmax of 63 ± 8 pg/mL plasma for 21 healthy women and men (mean ($\pm$ SD) age of 41 ± 10 years). reported a mean ($\pm$ SD) plasma Cmax of 53 ± 9 pg/mL plasma for 10 healthy men (21 – 33 years). reported a mean ($\pm$ SD) serum Cmax of 101 ± 49 pg/mL in 18 healthy men and women (mean age

29 years) and 35 ± 15 pg/mL serum in 18 healthy older men and women (mean age 60 years), with no subject having a level above 200 pg/mL. A plasma C_{max} of ~ 55 pg/mL for 12 healthy men (21 – 27 years) can be obtained from Figure 3 of [REDACTED] and a serum C_{max} of ~ 75 pg/mL for 12 healthy women (25 – 35 years) obtained from Figure 1 of [REDACTED] reported a mean ($\pm$ SD) serum C_{max} for mixed-sex groups of 63 ± 9 pg/mL at age 15 – 20 years and 29 ± 6 pg/mL at 70 – 90 years, though these values are based on a single measurement between 23:00 and 01:00 hr (adults in the age groups 20 – 35, 35 – 50, and 50 – 70 years did not show significant differences). Recently, [REDACTED] reported a mean plasma C_{max} for endogenous melatonin of 47 pg/mL for 27 older women and men (mean age ~ 74 years) considered to have low endogenous melatonin level. The data from the above 6 studies give an unweighted mean and median plasma / serum C_{max} for endogenous melatonin of 58 pg/mL and 55 pg/mL, respectively.

Dividing the mean and median C_{max} values (3350 pg/mL and 3510 pg/mL, respectively) following ingestion of a 3 mg dose of IR melatonin by the mean and median values for endogenous C_{max} (58 pg/mL and 55 pg/mL, respectively) gives an ~ 58- to 63-fold (~ 60-fold) increase. Although this estimate is based on data from multiple studies, none of which administered melatonin at bedtime, support for the size of the value is provided by the study of [REDACTED] which measured both endogenous C_{max} and C_{max} following administration up to 4 mg melatonin⁹ at bedtime to older women and men (mean age ~ 74 years).

In summary, the above data indicates that a 3 mg oral dose of immediate-release melatonin can be expected to result in a C_{max} of ~ 3400 pg/mL. This value is ~ 60-times the peak nocturnal (endogenous) plasma melatonin C_{max}, though both values are subject to considerable inter-individual variation. Linearity of C_{max} with increasing doses of oral immediate-release melatonin is discussed in [Section 2.5.3.1.5 Linearity](#) (Pharmacokinetics).

2.5.3.1.1.3 AUC

A crossover RCT ([REDACTED]) in which 6 men and 6 women (mean ($\pm$ SD) age 37 ± 8 years) in a fasting state ingested 2 and 4 mg IR melatonin reported mean ($\pm$ SD) AUC_(0-∞) values of 238 ± 150 and 531 ± 267 ng·min/mL, suggesting a value of ~ 385 ng·min/mL for a 3 mg dose. The linearity of the AUC and other PK parameters reported by this study are reviewed in [Section 2.5.3.1.5 Linearity](#) (Pharmacokinetics).

A cohort study [REDACTED] in which groups (n = 20) comprising an equal number of healthy men and women (20 – 37 years) ingested 3 mg melatonin powder reported a

[REDACTED]

mean AUC_{0-6h} of $269,110^{10}$ $\mu\text{mol}\cdot\text{min}/\text{L}$. The linearity of the AUC and other PK parameters reported by this study are reviewed in [Section 2.5.3.1.5 Linearity](#) (Pharmacokinetics).

A crossover RCT () reported an $AUC_{(0-\infty)}$ of 18.41 $\text{pmol}/\text{mL}\cdot\text{h}$ after ingestion of 5 mg melatonin (fast-release) by 15 healthy younger men.

An cohort study () reported AUC a value of 684 $\text{ng}/\text{mL}\cdot\text{min}$ in healthy younger men and women in fasting state following ingestion of 6 mg IR melatonin. This study is reviewed in detail in [Section 2.5.3.1.8 Pharmacokinetic drug interactions affecting melatonin](#)).

A cohort study () in which 10 younger women ($22 - 33$ years) and 8 older women ($46 - 59$ years) in fasting state ingested 6 mg IR melatonin found a mean ($\pm$ SD) AUC_{0-5h} to be comparable in the 2 groups (19.6 ± 11.2 vs. 20.6 ± 17.7 $\text{ng}\cdot\text{h}/\text{mL}$, respectively). Values ranged from 2.6 to 39.7 $\text{ng}\cdot\text{h}/\text{mL}$, and from 3.1 to 53.1 $\text{ng}\cdot\text{h}/\text{mL}$, in the 2 groups.

A systematic review of the clinical PK of melatonin () presents AUC data from 15 studies involving single oral doses in the range 0.25 to 80 mg. AUC ranged between 6.56×10^{10} $\text{pg}/\text{mL}\cdot\text{min}$ (dose 1 mg in men and women;) and $14,160$ $\text{pg}/\text{mL}\cdot\text{min}$ (dose 0.25 mg in men;). A cohort study () applying a multiple dosage regimen, reported an AUC of 31.3×10^6 $\text{pg}/\text{mL}\cdot\text{min}$.

A cohort study () in which 250 μg deuterium-labelled (D_7) melatonin (oral solution) was ingested during fasting by younger men and women (6 of each sex) found AUC (and C_{max}) in the women to be ~ 2.5 -times higher than in the men (mean ($\pm$ SD) AUC 701 ± 645 vs. 236 ± 107 $\text{pg}\cdot\text{h}/\text{mL}$, respectively). Due to the large variation in AUC (and C_{max}), particularly in the women, it is unlikely that the mean values for women are significantly different to those for men. A more detailed review and assessment of the findings of this study are presented in [Section 2.5.3.1.6.2 Sex](#) (Intrinsic factors affecting melatonin metabolism).

A cohort study () in which groups of $4 - 5$ healthy younger men and women (from a pool of 12 men and women) ingested 2 formulations of 2 mg IR melatonin in the fed and fasting state found AUC to be greater ($\sim 55\%$ and $\sim 115\%$) in the fed vs. fasting state (C_{max} was $\sim 29\%$ and $\sim 147\%$ greater in the fed vs. fasting state); T_{max} did not differ significantly in the fed vs. fasting state for either formulation (or between formulations). A more detailed review and assessment of the findings of this study are presented in [Section 2.5.3.1.7.1 Food](#) (type and timing of meals) (Intrinsic factors affecting melatonin metabolism).

A cohort study () including 33 volunteers ($6 - 31$ years) found that pre-pubertal subjects (mean age 8.4 years) had a significantly lower AUC than adults ($15,054$ vs. $22,614$ $\text{pg}/\text{mL}\cdot\text{min}$), with pubertal subjects having an intermediate value. No difference between the sexes was observed.

In summary, the above data indicate that 3 and 6 mg oral dose of immediate-release melatonin can be expected to result in AUC values of ~ 380 and ~ 680 $\text{ng}/\text{mL}\cdot\text{min}$, though values are subject to considerable inter-individual variation. Linearity of AUC with increasing doses of oral IR melatonin is discussed in [Section 2.5.3.1.5 Linearity](#) (Pharmacokinetics).

2.5.3.1.1.3 Absorption efficacy and bioavailability

A crossover RCT [REDACTED] found that after ingestion of 5 mg fast-release melatonin by 15 healthy male subjects (20 – 35 years), 3.4 mg of 6-hydroxymelatonin sulphate (the primary melatonin metabolite) was recovered from urine. As this metabolite typically accounts for ~ 70% (55 – 80%) of the melatonin excreted in the urine (and essentially all melatonin is excreted via the urine; see [Section 2.5.3.1.4 Excretion](#)) the data of [REDACTED] suggest essentially complete absorption of melatonin.

Based on a review of data for plasma melatonin concentration and urinary melatonin metabolites collated from several studies of *i.v.* or oral administration of melatonin to humans, [REDACTED] suggested that oral melatonin undergoes extensive first-pass metabolism, limiting its oral bioavailability. Subsequent studies have reported values for bioavailability in individual subjects in the range 1 to 56%. Two studies ([REDACTED] [REDACTED]) reporting mean values in the range 9 – 16%, are considered of particular importance as they are 2 of the largest and involved both men and women.

[REDACTED] calculated bioavailability values in the range 10 to 56% (mean 33%) for 4 healthy men administered 20 µg melatonin *i.v.* and 500 µg melatonin orally in a cross-over study.

[REDACTED] reported the bioavailability of an oral dose (solution) of 250 µg deuterium-labelled (D_7) melatonin ingested by 6 men and 6 women (healthy subjects aged 22 – 35 years) to range from 1 to 37%, with a mean of $8.6 \pm 3.9\%$ for males and $16.8 \pm 12.7\%$ for females (12.7% for both sexes).

[REDACTED] reported the absolute bioavailability of oral doses of 2 and 4 mg melatonin (formulated as a 2 mg tablet¹¹) given to 6 men and 6 women (healthy volunteers; mean age ($\pm$ SD): 37 ± 8 years) in a cross-over study to be $14.3 \pm 7\%$ and $15.9 \pm 6\%$ for the two doses, respectively (separate means were not presented for men and women). The data of [REDACTED] is considered the most relevant as their study included men and women and administered melatonin at doses, and with a formulation, comparable to those of the Applicant's product.

A recent study [REDACTED] reported a median bioavailability of 2.5% following ingestion of 10 mg IR melatonin by 12 healthy men. The authors had no explanation for what they considered to be the low bioavailability observed.

In summary, oral melatonin is efficiently (almost completely) absorbed from the gastrointestinal (GI) tract, though bioavailability is low (~ 15%) due to extensive first-pass metabolism. Variability in the extent of first-pass metabolism appears to be the primary process underlying inter-individual variability in bioavailability, though variability in the efficacy of absorption of melatonin from the GI tract may play a role.

2.5.3.1.2 Distribution

2.5.3.1.2.1 Plasma protein binding

[REDACTED] found protein mean ($\pm$ SE) binding of $60.7 \pm 4.8\%$ at 37°C when the binding of 3H -melatonin to human plasma was studied *in vitro* using equilibrium

[REDACTED]

dialysis. The proportion of ^3H -melatonin bound was constant over the range tested¹². The apparent lowest concentration tested is relatively close (only ~ 35% higher) to that expected following ingestion of the standard dose (3 mg) of the Applicant's product (i.e. plasma C_{max} of ~ 3400 pg/mL; see [Section 2.5.3.1.1.2 C_{max}](#)), thus the study's findings are also applicable to the maximum recommended dose (6 mg) for the Applicant's product. When ^3H -melatonin was dialysed to equilibrium against solutions of separate human plasma proteins (albumin, α -, β -, and γ -globulin, fibrinogen) at concentrations (of the proteins) comparable to those found in human blood, only albumin bound melatonin (60.6 $\pm$ 3.5%). Likewise, electrophoresis of rat plasma indicated albumin to be the only detectable plasma protein that bound ^3H -melatonin.

found protein binding of 47% (constant over the 8-fold range of concentrations studied) when ^3H -melatonin was incubated with human plasma in equilibrium dialysis experiments, though this value is for physiological concentrations¹³ (i.e. tens-to-hundreds of times below C_{max} for the Applicant's product). Melatonin (like several other circulating methoxyindoles) had low affinity for its plasma binding site(s), and appeared to bind to albumin only¹⁴. The authors considered their data to show that melatonin reversibly binds to high-capacity, low-affinity bindings sites in the plasma.

found protein binding of 53% at 37°C (pH 7.4) when ^3H -melatonin at "physiological melatonin concentrations below 1 nmol/L" (~ 230 pg/mL) was incubated with human serum proteins in equilibrium dialysis experiments. Melatonin was found to bind albumin with low affinity (1.5 $\pm$ 0.1 mmol/L) and α 1-acid glycoprotein with high affinity (27 $\pm$ 3 mmol/L). Binding to other serum proteins, γ -globulins, and lipoproteins was not significant. Melatonin serum binding was characterised by a saturable component (resulting from the high-affinity binding to α 1-acid glycoprotein), and a non-saturable component (resulting from the low-affinity binding to albumin). The number of binding sites was 0.36/molecule of α 1-acid glycoprotein, indicating that only a fraction of α 1-acid glycoprotein bound melatonin. The authors suggested that the high-affinity binding to α 1-acid glycoprotein might result from a potentiation of the binding interaction by albumin, and that the amount of melatonin bound in plasma might vary according to the α 1-acid glycoprotein concentration. As binding to α 1-acid glycoprotein was saturable even at very low (physiological) melatonin concentrations, it can be expected to have a negligible role in relation to the plasma protein binding of typical therapeutic doses of melatonin.

In summary, the plasma protein binding of exogenous melatonin is expected to be in the range 50 – 60%, with the upper value more representative of binding associated with the peak plasma melatonin concentrations achieved during the first 1 – 2 h post-ingestion, and the lower value more representative of melatonin concentrations approaching physiological levels. Melatonin binds primarily to albumin, a high-capacity, low affinity plasma binding protein, with limited binding to other plasma proteins, though high-affinity binding to a minor fraction of circulating α 1- acid glycoprotein has been reported. Melatonin is not strongly or extensively bound to plasma proteins, therefore significant effects of protein binding on melatonin PK are not expected.

2.5.3.1.2.2 General distribution

found protein binding of 47% (constant over the 8-fold range of concentrations studied) when ^3H -melatonin was incubated with human plasma in equilibrium dialysis experiments, though this value is for physiological concentrations¹³ (i.e. tens-to-hundreds of times below C_{max} for the Applicant's product). Melatonin (like several other circulating methoxyindoles) had low affinity for its plasma binding site(s), and appeared to bind to albumin only¹⁴. The authors considered their data to show that melatonin reversibly binds to high-capacity, low-affinity bindings sites in the plasma.

Due to its small size and lipophilic, non-ionised nature, melatonin can be expected to rapidly move across cell membranes and thus rapidly move into and out of tissues and organs. Melatonin has been detected in multiple extrapineal tissues (including the brain, retina, lens, cochlea, Harderian gland, respiratory epithelium, skin, gastrointestinal tract, liver, kidney, thyroid, pancreas, thymus, spleen, leukocytes, carotid body, reproductive tract, and endothelial cells), and is also present in essentially all biological fluids (including cerebrospinal fluid (CSF), saliva, bile, synovial fluid, amniotic fluid, and milk); in several of these fluids, melatonin concentrations exceed those in the blood ([REDACTED]). The level in the CSF is higher than in the serum ([REDACTED]).

The distribution of melatonin after oral administration (80 mg IR) is best described using a bi-exponential equation with an absorption constant (k_a) of 1.72 h^{-1} (half-life of 0.40 h) and an elimination constant (k_{el}) of 0.87 h^{-1} (half-life of 0.80 h). This indicates that the distribution obeys either a one-compartment open model or a two-compartment open model with very rapid exchange between the compartments [REDACTED]. [REDACTED] found melatonin clearance from blood to show a biphasic pattern of first-order kinetics.

No studies investigating the level of melatonin in different organs after melatonin intake, or the possible accumulation of melatonin in different organs after chronic melatonin treatment were identified in the literature. However, systemic clearance of melatonin is rapid: plasma $T_{1/2}$ is ~ 45 minutes, and the large majority of a typical oral dose is eliminated within ~ 5 h (see [Section 2.5.3.1.4 Excretion](#)).

2.5.3.1.2.3 Blood-brain barrier

Melatonin readily crosses the blood-brain barrier, as demonstrated in a study in which positron emission tomography (PET) was combined with PK measurements of radiolabelled melatonin administered *i.v.*¹⁵ in a healthy male volunteer ([REDACTED]). The plasma / CSF melatonin ratio was similar for endogenous melatonin and following ingestion of 500 mg melatonin, indicating that melatonin enters the CSF via the blood [REDACTED].

2.5.3.1.2.4 Transplacental distribution

[REDACTED] noted that studies in rats, sheep and rhesus monkeys have shown that melatonin rapidly moves from the maternal circulation to the fetal circulation.

Following ingestion of 3 mg melatonin¹⁶ by 33 pregnant women 1, 2, 3 or 4 h prior to an elective cesarean section, serum melatonin concentration in the umbilical vein at the time of delivery was found to be closely correlated ($r = 0.924$, $p < 0.001$) with that in the maternal vein (venous blood) (Figure 5 of the study report) ([REDACTED]). The pattern of change in melatonin concentration in the umbilical vein and artery mirrored (though were ~ 15% and 35% lower, respectively) the rapid and significant (~ 1000-fold over the baseline (daytime) level) increase, and subsequent relatively rapid decrease in maternal melatonin concentration over the first 4 h after ingestion of melatonin by 9 full-term pregnant women (Figures 3 and 4 of the study report). These data indicate that in humans melatonin rapidly moves from maternal circulation to the fetal circulation, and that the maternal and fetal circulation are in tight equilibrium.

Text noting that exogenous melatonin readily crosses the human placenta is included under the heading [Pregnancy in Section 4.6 of the proposed Summary of Product Characteristics \(SmPC\)](#) for the Applicant's product, while text noting that melatonin readily crosses the placenta, and that the level in umbilical blood of full-term babies closely correlates with, and is only slightly lower (~ 15 – 35%) than, that of their mother following ingestion of a 3 mg dose, is included under the heading [Distribution in Section 5.2](#).

2.5.3.1.2.5 *Distribution into mother's milk*

Endogenous melatonin is present in human milk. [REDACTED] found the level to be essentially undetectable during the day and to peak mid-to-late night at roughly 35% of the peak (night-time) maternal serum concentration. Literature data for the distribution of exogenous melatonin or its metabolites in human milk were not identified. [REDACTED]

[REDACTED] found saliva melatonin concentration following ingestion of melatonin to be approximately one-third of that in serum, a value consistent with the milk:serum ratio for endogenous melatonin reported by Illnerová et al., and it could be speculated that a comparable ratio may apply to exogenous melatonin.

Text included under the heading [Lactation in Section 4.6 of the proposed SmPC](#) notes that endogenous melatonin is secreted in human milk, though there is insufficient data on the excretion of melatonin / metabolites in human milk with use of melatonin. It further notes (with reference to Section 5.3) that available pharmacodynamic / toxicological data in animals have shown excretion of melatonin / metabolites in milk.

2.5.3.1.3 *Metabolism*

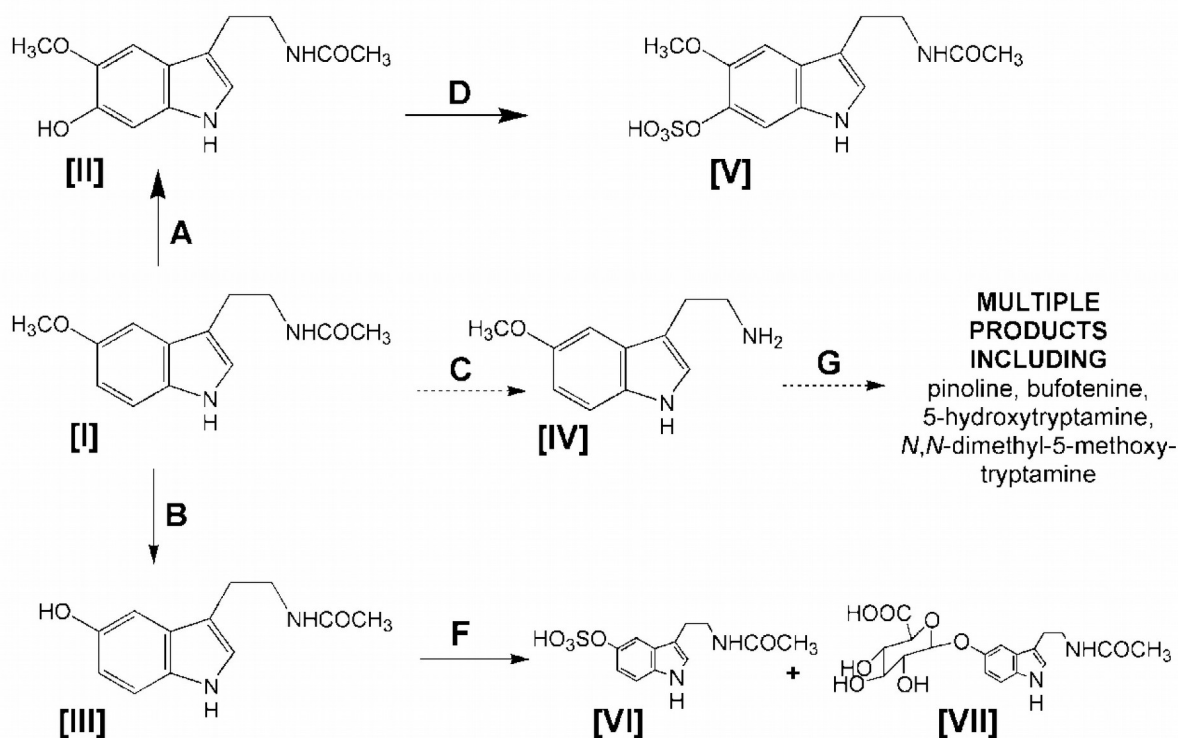
The following summary of the metabolism of melatonin is based primarily on data reported or reviewed by [REDACTED]

[REDACTED] Melatonin is primarily (~ 90%) metabolised in the liver, mainly by the cytochrome P450 system enzymes CYP1A1 and CYP1A2 to yield predominantly 6-hydroxymelatonin. Based on the assessment of human urine, ~ 70% of 6-hydroxymelatonin undergoes sulphate conjugation to yield 6-hydroxymelatonin sulphate (6-sulphatoxy-melatonin) and ~ 30% undergoes glucuronide conjugation to yield 6-hydroxymelatonin glucuronide (see [Figure 2.5.3.1.3 The common metabolic pathways of melatonin](#))

Minor pathways of melatonin metabolism include O-demethylation (mediated by CYP2C19), yielding N-acetylserotonin (N-acetyl-5-hydroxytryptamine), which undergoes sulphate or glucuronide conjugation; de-acetylation to 5-methoxytryptamine (which can be further metabolised to a range of metabolites); and hydroxylation to cyclic 2-hydroxymelatonin and acyclic 3-hydroxymelatonin.

In the CNS, oxidative pyrrole-ring cleavage predominates and 6-hydroxymelatonin is not detected. The primary cleavage product is N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK). Several different reactions lead to the formation of AFMK, and this pathway accounts for ~ 30% of melatonin metabolism in the CNS. AFMK is converted into N1-acetyl-5-methoxykynuramine (AMK). AFMK and AMK can react with reactive oxygen- and nitrogen species, and thus may potentially help protect the CNS from oxidative stress [REDACTED]

Figure 2.5.3.1.3 The common metabolic pathways of melatonin



Melatonin (molecule I) undergoes 6-hydroxylation (process A) to 6-hydroxymelatonin (II), which is sulphated (D) to 6-hydroxymelatonin sulphate (V), and by O-methylation (B) to N-acetylserotonin (N-acetyl-5-hydroxytryptamine) (III) which is further conjugated (F) to its sulphate (VI) and glucuronide (VII). A minor pathway is deacetylation (C) to 5-methoxytryptamine (IV) which can be further metabolized (G) to a range of minor metabolites.

Some of the individual studies contributing data to the above summary of the pathways of metabolism of melatonin, but also demonstrating the rapid rate of metabolism of melatonin are summarised below.

██████████ reported that after ingestion of 5 mg melatonin (described as fast-release) by 15 healthy male subjects (20 – 35 years), 3.6 mg of 6-hydroxymelatonin sulphate was recovered from the urine, representing ~ 68% of the ingested melatonin dose. ~ 87% of the 6-hydroxymelatonin sulphate recovered in the urine was eliminated between 0 and 3 h, indicating rapid metabolism of melatonin¹⁷ (and also rapid absorption of melatonin and rapid excretion of its primary metabolite). The rapid rate of metabolism of melatonin indicated by the data of ██████████ is supported by the study of ██████████. Following bolus injection of 42 µg of [¹¹C]melatonin to a healthy male, plasma radioactivity ([¹¹C]melatonin plus radiolabelled metabolites already formed) peaked after 3.5 minutes. Immunoreactive plasma melatonin peaked after 3.5 minutes; immunoreactive plasma 6-hydroxymelatonin sulphate started to rise after ~ 5 minutes and had already peaked after 20 minutes (see [Figure 1 of the study report](#)). The plasma radioactivity curve was super-imposable on that obtained by summation of melatonin and 6-hydroxymelatonin sulphate molar concentrations, indicating that 6-hydroxymelatonin sulphate is the major human metabolite.

A subsequent study (██████████) in which 0.5 µg/kg melatonin was infused i.v. over a 10-minute period starting at 10:00 hr to 9 men and 7 women (18 – 31 years)

a plasma $T_{1/2}$ of 42.4 ± 2.9 minutes (mean $\pm$ SEM) for 5 men and 9 women (with age-related insomnia but otherwise healthy; mean age 70 years; range 57 – 79) following ingestion of 0.5 mg melatonin formulated as a gelatine capsule (considered IR). [REDACTED] reported reported mean plasma $T_{1/2}$ values of 33, 41, 35 and 47 minutes, respectively for 0.1, 0.5, 1.0, and 5.0 mg oral doses of melatonin formulated as a gelatine capsule (considered IR) given to 21 men and 11 women (healthy; aged 18 – 38 years) in a cross-over study; the values did not differ significantly between the treatment groups (see Table 3.5.3.1.5-1). [REDACTED] reported a mean ($\pm$ SD) serum $T_{1/2}$ of 60.8 ± 13.2 minutes and 65.0 ± 11.3 minutes, respectively, for 2 mg and 4 mg oral doses of IR melatonin given to 6 men and 6 women (healthy; mean age ($\pm$ SD): 37 ± 8 years) in a cross-over study. The values were not significantly different, and were not significantly different to that (59.5 ± 7.2 minutes) for a 2 mg dose administered *i.v.* to the same subjects (see Table 3.5.3.1.5-2.). [REDACTED] reported a mean serum $T_{1/2}$ of 38 minutes for 15 men (young, healthy adults) following ingestion of 5 mg fast-release melatonin. [REDACTED] reported a serum $T_{1/2}$ of 53 minutes (Figure 2 of the study report) for 5 men (young, healthy adults) following ingestion of 80 mg crystalline melatonin in gelatine capsules, a formulation considered IR.

In addition, [REDACTED] reported a mean ($\pm$ SE) serum terminal $T_{1/2}$ of 43.6 ± 1.5 minutes for 13 male and 9 female healthy volunteers (30 – 63 years) following infusion of 10 μ g melatonin; melatonin clearance showed biphasic, first-order (linear) kinetics. [REDACTED] reported a mean salivary $T_{1/2}$ of 50 minutes for 22 women (12 with insomnia, all otherwise healthy; mean age ($\pm$ SD) $\sim 65 \pm 7.5$ years) following ingestion of 5 mg melatonin formulated as a gelatine capsule (considered IR).

The above studies involving intake of single oral doses of IR melatonin in the range 0.1 to 80 mg reported serum / plasma $T_{1/2}$ values of 33, 35, 36, 38, 41, 42, 45, 47, 53, 61, and 65 minutes (median 42 minutes; unweighted mean 45 minutes), with values for doses in the range of those (3 or 6 mg) proposed for the Applicant's product being 38, 47, and 65 minutes (unweighted median 47 minutes; unweighted mean 50 minutes), with a saliva $T_{1/2}$ of 50 minutes. A systematic review of the clinical PK of melatonin [REDACTED] included blood $T_{1/2}$ values from 5 additional studies involving administration of doses of IR melatonin in the range 3 – 6 mg. When combined with the 3 relevant values reported by the Applicant, an unweighted median of 49 minutes and an unweighted mean of 57.5 minutes are obtained. Using data from 18 studies in which melatonin at doses up to 100 mg was administered orally or *i.v.* (no *i.v.* dose exceeded 2 mg), [REDACTED] estimated blood melatonin $T_{1/2}$ to be 45 minutes.

Based on the above, text has been included under the heading [Elimination in Section 5.2 of the proposed SmPC](#) stating that plasma elimination half-life ($T_{1/2}$) is ~ 45 minutes (normal range $\sim 30 - 60$ minutes) in healthy adults.

Urinary and faecal excretion and their relative importance

After *i.v.* administration of 2.1 μ g β^{14} C-melatonin to 5 men > 90% of the administered radioactivity was recovered in the urine during the first 24 h, with the remaining radioactivity recovered during the subsequent 24 h ([REDACTED]).

[REDACTED] reported that after ingestion of 5 mg fast-release melatonin by 15 healthy male subjects (20 – 35 years), 3.6 mg of 6-hydroxymelatonin sulphate was recovered from urine, representing $\sim 68\%$ of the ingested melatonin dose. As 6-hydroxymelatonin sulphate accounts for $\sim 70\%$ of melatonin metabolites excreted in the

urine¹⁹, urinary excretion appears to have accounted for ~ 95% of excretion of melatonin metabolites in this study. The finding that ~ 87% of the 6-hydroxymelatonin sulphate recovered in the urine was eliminated between 0 and 3 h indicates not only very rapid absorption and metabolism of melatonin but also very rapid elimination of its primary metabolite, 6-hydroxymelatonin.

Based on the above (plus relevant information in [Section 2.5.3.1.3 Metabolism](#)), text has been included under the heading [Elimination in Section 5.2 of the proposed SmPC](#) stating that melatonin metabolites are mainly eliminated via urine, ~ 90% as sulphate and glucuronide conjugates of 6-hydroxymelatonin.

The efficient metabolism of melatonin is confirmed by the very small proportion of a melatonin dose excreted as unchanged melatonin via urine (the predominant route of excretion). [REDACTED] reported that < 1% of a 23 µg *i.v.* dose of deuterium-labelled (D₇) melatonin (isotonic solution) was excreted unchanged in the urine during the first 12 h in 6 men and 6 women (healthy, 22 – 35 years). The study also examined the PK of an oral 0.25 mg dose of melatonin (solution) in the same subjects. The proportion of the oral dose excreted unchanged in the urine was not specifically reported, though [REDACTED] stated that the clearance of unchanged melatonin observed (< 1%) was in accordance with other reports (unspecified). [REDACTED] ~ 0.01% of a 100 mg oral dose of IR melatonin to be excreted unchanged in the urine during the first 6 h in 5 healthy men aged 25 – 48 years. [REDACTED] reported that 0.4% of a 100 mg oral dose of melatonin (solution) was excreted unchanged in the urine over 24 h, with 75% of this quantity excreted during the first 6.5 h after ingestion, by a healthy male (44 years). The duration of the collection periods (≥ 8 plasma melatonin half-lives of 45 minutes) in both studies are considered adequate to ensure that essentially all the melatonin that might have been eliminated unchanged in the urine was collected. Although the above data are for a small *i.v.* dose, or a very large oral dose, of melatonin, and are primarily for men, they are considered to indicate that < 1% is a realistic estimate of the maximum quantity of unchanged melatonin excreted in the urine.

In summary, the plasma elimination half-life (T_{1/2}) for immediate-release melatonin in healthy adults (including the elderly) is ~ 45 minutes (normal range ~ 30 – 60 minutes) and is essentially constant at oral doses up to 100 mg. The rapid elimination of exogenous melatonin is made possible by its rapid, primarily hepatic, metabolism, and the subsequent rapid conjugation and elimination of its metabolites (~ 90% of which are sulphate and glucuronide conjugates of 6-hydroxymelatonin) via the urine. Less than ~ 1% of an oral dose of melatonin is excreted unchanged in urine. Faecal excretion of melatonin and its metabolites following ingestion of typical therapeutic doses of melatonin is expected to be negligible.

2.5.3.1.5 Linearity

The first 2 studies ([REDACTED]) of the 4 studies summarised below are considered to provide the most relevant linearity data as they involved oral doses in the range 0.1 – 5 mg), used formulations with PK properties characteristic of IR, and had a cross-over design (i.e. all doses were tested in the same subjects).

Table 3.5.3.1.5-1

Pharmacokinetic data for plasma melatonin (Table 1)

Table 1. Mean (standard deviation) time to peak plasma level expressed in hours, peak plasma level (pmol/L), and elimination half-life in hours for each of the four dosage groups

Group (mg)	Absorption (hr)	Peak (pmol/L)	Half-life (hr)	Cmax values calculated as pg/mL
0.1	1.25 (.48)	536 (421)	0.55 (.69)	124
0.5	0.88 (.33)	3,054 (3,022)	0.68 (.75)	709
1.0	0.78 (.47)	5,839 (6,017)	0.59 (.33)	1355
5.0	0.97 (.75)	23,982 (16,544)	0.79 (.20)	5564

indicating clearance of melatonin from the plasma / body is not expected to be impaired with oral doses several times the upper (4 mg) dose tested.

Table 3.5.3.1.5-2

Pharmacokinetic data for serum melatonin (Table 1 of [REDACTED])

Table I Pharmacokinetics of Three Doses of Melatonin

Dose	AUC (ng•min/ml)	C _{max} (pg/ml)	t _{max} (min)	Half-Life (min)	Bioavailability
2 mg oral	237.77 ± 149.79	2175 ± 1645	52.0 ± 31.5	60.8 ± 13.2	0.143 ± 0.07
4 mg oral	530.57 ± 267.29	5766 ± 2731	60.3 ± 31.6	65.0 ± 11.3	0.159 ± 0.06
2 mg IV	1631.61 ± 425.74	96,850 ± 55,024	1.79 ± 1.41	59.5 ± 7.2	1.00 ± 0.0
p-value ^a	0.0001	0.0001	0.0001	0.385	0.0001

AUC, area under the serum concentration versus time curve from zero to infinity; t_{max}, time to peak concentration; C_{max}, peak serum concentration.
a. IV versus either oral phase.

The following 2 studies involved melatonin formulations less comparable to the Applicant's product, had relatively small numbers of subjects, and did not have a cross-over design (the latter factors can be expected to influence the robustness of their findings considering the large inter-individual variability of melatonin PK). Both studies found strong linearity for doses in the range 0.4 to 4 mg.

[REDACTED] gave 1 mg or 3 mg melatonin as a powder (no further details), and 1 mg melatonin in a soft gelatine capsule (not discussed here), to 3 groups (n = 20) of healthy men and women (n = 30 for both sex; age range 20 – 37 years). Blood samples for determination of plasma melatonin concentration were collected immediately before and at 12 time-points during a 6 h time-window after intake of melatonin. Mean plasma C_{max} was ~ 3.01-fold greater (2405 vs. 799 pg/mL; p < 0.001) and mean AUC_{0-6h} was 2.97-fold greater (269,110²⁴ vs. 90,516 μmol•min/L; p < 0.001) for the 3 mg dose compared to the 1 mg dose, indicating a directly-proportional, linear dose-response relationship.

A study by [REDACTED] is considered relevant despite only 25% of each of the 2 doses tested being in the form of an IR tablet (the remaining 75% was in the form of a sustained-release tablet). 0.4 or 4 mg doses of melatonin, or placebo, were ingested by 3 groups (n = 8 – 10) of healthy elderly subjects (~ 74 years; ~ 75% women). Blood samples for determination of serum melatonin concentration were collected before and at 24 time-points during a ~ 18 h time-window after intake of melatonin or placebo at the end of the 42-day intervention period. [Table 2 of the study report](#), which summarises the PK data is reproduced below. Mean serum C_{max} was ~ 9.87-fold greater (p < 0.001) and AUC ~ 10-fold greater²⁵ (p = 0.002) with the 10-fold greater dose (4 mg vs. 0.4 mg), indicating a directly-proportional dose-response relationship. T_{max}, serum T_{1/2}, mean apparent clearance (CL/F), and mean apparent volume of distribution (V/F) were similar for the low and high dose groups (p ≥ 0.4).

Table 3.5.3.1.5-3

Pharmacokinetic data for serum melatonin (Table 2 of [REDACTED])

Note: endogenous melatonin PK was measured at Visit 1, and PK following ingestion of melatonin at Visit 2.

Table 2

Comparison of pharmacokinetic parameters of exogenous melatonin in low dose and high dose groups.

Parameters	Low Dose Mean (SE)		High Dose Mean (SE)	
	Visit 1	Visit 2	Visit 1	Visit 2
CL/F, L/hr	--	379 (89.4)	--	478 (116)
V/F, L	--	1035 (304)	--	1602 (578)
Ka, hr ⁻¹	--	2.6 (0.89)	--	1.3 (0.30)
t _{1/2} , hr	1.7 (0.16)	1.8 (0.19)	1.6 (0.16)	2.1 (0.34)
T _{max} , hr	4.7 (0.96)	1.3 (0.19)	5.1 (1.4)	1.5 (0.24)
C _{max} , pg/mL	52 (8.1)	405 (93.0)	61 (11)	3999 (700)
T _{>50pg/mL} , hr	2.0 (1.1)	6.4 (0.65)	2.5 (1.5)	10.0 (0.89)
AUC _{0-last} , pg/mL•hr	337 (64)	1577 (373)	418 (73)	12039 (2268)
AUC _{0-∞} , pg/mL•hr	350 (65)	1595 (374)	438 (79)	12123 (2277)

CL/F, apparent total clearance; V/F, apparent volume of distribution; Ka, first-order absorption constant; t_{1/2}, elimination half-life; T_{max}, time to reach maximum concentration; C_{max}, maximum concentration; T_{>50pg/mL}, time duration above 50 pg/mL; AUC_{0-last}, area under the concentration-time curve up to last observed data; AUC_{0-∞}, area under the concentration-time curve extrapolated to infinity.

In summary, the above data indicate a linear dose-response relationship for serum / plasma melatonin concentration (C_{max} and AUC) following ingestion of immediate-release melatonin doses in the range 0.1 – 5 mg. Although the upper limit of this range is 20% below the upper recommended dose of the Applicant's product, the data does not suggest that linearity changes abruptly with doses above 5 mg. Based on the above, text has been included under the heading [Elimination in Section 5.2 of the proposed SmPC](#) stating that plasma C_{max} and AUC increase in a linear manner for oral doses of IR melatonin in the range 3 – 6 mg, whereas T_{max} and plasma T_{1/2} remain constant.

2.5.3.1.6 Intrinsic factors affecting melatonin pharmacokinetics

Intrinsic factors that may influence the PK of oral melatonin are addressed in the following sections: they are age, sex, race, genotype, hepatic impairment, and renal impairment.

2.5.3.1.6.1 Age (adults)

Lower peak night-time plasma endogenous melatonin concentration (C_{max}) has been observed in elderly persons ([REDACTED]) and is attributed to reduced synthesis.

The study of [REDACTED] was the only literature study identified that directly compared the PK of oral melatonin (0.3 mg IR) in younger *and* older adults of both sexes.

Melatonin PK (summarised in *Table 2.5.3.1.6.1-1*.) was generally comparable in 6 men and 4 women with a mean age of 26 years (range: 20 – 32 years) and healthy, compared to 4 men and 6 women with a mean age of 59 years (range: 49 – 73 years) (healthy status unspecified). T_{max} was the same for the 2 age groups. C_{max} and AUC_{0-7h} tended to be higher in the older subjects; differences were not statistically significant, though in the case of C_{max} (p = 0.1) in particular this may be due to the much wider range of values for the elderly subjects coupled with small sample size. The mean time for serum melatonin concentration to return to the daytime value (< 5 pg/mL) was the same in the younger and older subjects, which indicates comparable serum T_{1/2} across age.

Table 2.5.3.1.6.1-1

Pharmacokinetic data for serum melatonin young and older adults (men and women) from the study of [REDACTED]

Values (except in the case of serum C_{max} range) are mean ± SD (n = 10 for both age groups).

Age group	C _{max} (pg/mL)	C _{max} range (pg/mL)	T _{max} (min)	AUC (pg·mL/h)	Hours > 5 pg/mL (h)
20 – 32	170.2 ± 22.0	142 – 205	48 ± 4.9	441.9 ± 121.1	6.4 ± 0.21
49 – 73	254.9 ± 145.7	76 – 486	45 ± 6.7	595.8 ± 312.1	6.6 ± 0.24

[REDACTED] also directly compared melatonin PK in younger and older subjects, though in women only: 10 healthy pre-menopausal women (mean age 27.5 years; range: 24 – 33 years) and 8 healthy post-menopausal women (mean age 51.4 years; range: 46 – 59 years). No significant differences in melatonin PK were seen (see Table 1 of the study report) following ingestion of 6 mg IR melatonin. More than 99% of the melatonin dose had been eliminated from the blood after 5 h. As observed in the study of [REDACTED] inter-individual variation tended to be greater among the older subjects²⁶.

In support of the limited data summarised above, PK data from several studies (summarised below) that involved only older persons can be compared to that for younger adults, though caution should be exercised when comparing data from studies with different designs and analytical procedures, and consideration should be given to possible regional variations in the normal range of values for PK parameters.

In [REDACTED] the shape of the plasma melatonin concentration-time curve (see Figure 2 of the study report) following ingestion of 0.5 mg IR melatonin by 5 men and 9 women with a mean age of 70 years (range 57 – 79 years) with age-related insomnia but otherwise healthy appears comparable to that of young adults. Plasma melatonin concentration had effectively returned to baseline after ~ 8 h, which is consistent with the findings of [REDACTED]. The plasma T_{1/2} of 42.4 ± 2.9 minutes (mean ± SE) is in good agreement with the mean values of 46 and 52 minutes reported by [REDACTED] and with the blood T_{1/2} of 45 minutes following oral and *i.v.* administration calculated in a systematic review of the clinical PK of melatonin ([REDACTED]).

26 Greater variability in the extent of first-pass metabolism, and in the efficacy of absorption from the gastrointestinal tract, were considered likely mechanisms.

In [REDACTED] the shape of the saliva²⁷ melatonin concentration-time curve (see Figure 2 of the study report) following ingestion of 5 mg IR melatonin by 22 women with a mean ($\pm$ SD) age of $\sim 65 \pm 7.5$ years (12 with insomnia, though all were otherwise healthy) appears comparable to that for plasma / serum melatonin concentration following ingestion of melatonin by young adults reported by [REDACTED] and [REDACTED].

[REDACTED] Salivary melatonin concentration was significantly higher than the endogenous level only during the first 7 h after ingestion of melatonin, and mean salivary $T_{1/2}$ was 50 minutes, both of which are in good agreement with the equivalent values for serum / plasma reported by Zhdanova et al., Markantonis et al., and [REDACTED].

In contrast to the above studies, [REDACTED] found plasma melatonin concentration to remain above normal ~ 13 h after ingestion of 3 mg IR melatonin by a group of 30 male and female insomniacs over 50 years old (healthy, though 15 with insomnia), and data in Figure 3 of their study report suggests a plasma $T_{1/2}$ of ~ 2 h.

[REDACTED] reported PK data for 0.4 and 4 mg doses of melatonin ingested by 2 groups ($n = 9 - 10$) of subjects with a mean age of ~ 74 years ($\sim 75\%$ women) and insomnia complaints (and 'low' endogenous melatonin levels), though as only 25% of each dose was IR melatonin (the remaining 75% was sustained release) the data is not considered.

In summary, the PK of oral immediate-release melatonin at doses in the range 0.3 – 6 mg is generally comparable in younger and older adults, though the range of values for a given PK parameter tends to be greater in the elderly. Consequently, no alternative dosing recommendations for elderly persons are considered warranted. Relevant text is included in [Sections 4.2 and 5.2 of the proposed SmPC](#) for the Applicant's product. The potential, in certain individuals, for the combination of a lower rate of absorption and a higher rate of elimination to result in relatively low (potentially sub-therapeutic) C_{max} / AUC values with the standard 3 mg dose is accounted for by the option to increase the dose to 6 mg if the standard dose does not adequately alleviate jet-lag. Relatively high C_{max} / AUC values expected with a combination of a higher rate of absorption and lower rate of elimination are not expected to be of clinical concern due to the rapid elimination of melatonin ($T_{1/2}$ of ~ 45 minutes) and the extensive safety data for oral melatonin in clinical trials (including jet-lag studies) involving older persons.

2.5.3.1.6.2 Sex

[REDACTED] noted that according to the literature, men appear to have higher CYP1A2 activity than women. As melatonin is predominantly metabolised by this isoenzyme, a relatively lower metabolism of melatonin in women could potentially give / contribute to greater bioavailability of exogenous melatonin in women compared to men.

Plasma PK data from [REDACTED] in which 250 μ g deuterium-labelled (D_7) melatonin (oral solution) was ingested by 6 men and 6 women (healthy) aged 22 – 35 years are summarised in Table 2.5.3.1.6.2-1. Mean values for plasma melatonin C_{max} and AUC for women were ~ 2.5 -times those for men, and F (bioavailability) was double, whereas T_{max} and plasma $T_{1/2}$ were comparable. However, due to the large variation in C_{max} , AUC, and F values, particularly in women, it is unlikely that the mean values for

women are significantly different²⁸ to those for men. Inspection of the individual concentration-time curves for plasma melatonin (Figure 2 of Fourtillan et al.) reveals that 4 of the 6 women had profiles generally comparable to those of men, whereas 2 women had a C_{max} and AUC about 3-times those of the other 4 women and of all the men. Thus the apparently greater C_{max}, AUC, and F in women may be a chance finding associated with the small sample sizes, though it cannot be discounted that a minority of women have relatively high values.

Table 2.5.3.1.6.2-1

Pharmacokinetic data for plasma melatonin in men and in women from the study of

Values are mean ± SD (n = 6 for both sexes).

Sex	C _{max} (pg/ml)	T _{max} (h)	AUC (pg·h/ml)	T _{1/2} (h)	F (%)
Men	244 ± 125	0.38 ± 0.14	236 ± 107	0.60 ± 0.10	8.6 ± 3.9
Women	624 ± 575	0.38 ± 0.14	701 ± 645	0.75 ± 0.24	16.8 ± 12.7

Using data for individual subjects reported by [REDACTED] comparable serum C_{max} values of 168 ± 23 and 174 ± 23 pg/mL, respectively, can be calculated for 6 men and for 4 women (healthy) with a mean (± SD) age of 25.9 ± 4.7 years following ingestion of 0.3 mg IR melatonin. In 4 men and 6 women (health status unspecified) with a mean age of 59.0 ± 10 years, serum C_{max} was 160 ± 94 and 318 ± 145 pg/mL, respectively (i.e., twice as high in women), though both the older men and older women showed C_{max} values markedly below and above those of the younger subjects.

[REDACTED] reported no difference in 24-h melatonin excretion (measured as urinary 6-hydroxymelatonin sulfate) in 13 men (36 ± 14 years) compared to 7 women (31 ± 12 years), all with delayed sleep-phase syndrome, when measured after 4 weeks intake of 5 mg melatonin²⁹ daily, suggesting comparable absorption efficacy.

A study ([REDACTED]) in which 0.5 µg/kg melatonin was infused *i.v.* over a 10-min period to 9 men and 7 women (healthy) aged 18 – 31 years (mean age ~ 27 years for both sexes) did not observe a significant effect of gender on melatonin PK parameters including mean (± SD) serum terminal T_{1/2} (0.82 ± 0.15 vs. 0.81 ± 0.12 h) and AUC (390 ± 173 vs. 384 ± 160 (pg·h/mL).

[REDACTED] noted that PK data (AUC, C_{max}, T_{max}, T_{1/2}) for 3 healthy women did not stand out from those of 12 healthy younger men following ingestion of 6 mg IR melatonin (this study is summarised under the heading *Oestrogens* in [Section 2.5.3.1.8 Pharmacokinetic drug interactions affecting melatonin](#)).

A number of other literature studies, including studies presented in other sections of this document, reporting PK data for oral melatonin enrolled both men and women, but did not reported separate values the sexes (or data for individuals).

[REDACTED]

A systematic review of the clinical PK of melatonin ([REDACTED]) concluded that no significant differences between the sexes have been observed.

In summary, the available data, although limited, do not suggest significant differences in the overall PK of immediate-release melatonin in men and women. It is possible that C_{max} and AUC (bioavailability) may be higher (potentially double) in women, though the large variability in melatonin PK in men and women precludes any firm conclusions regarding C_{max} and AUC based on the limited data available. The data does not indicate that melatonin metabolism and excretion (as reflected by plasma / serum T_{1/2}) differs significantly between men and women. The available data is not considered adequate to support separate dose recommendations for men and women. Relevant text is included in [Section 5.2 of the proposed SmPC](#).

2.5.3.1.6.3 Race

No literature studies specifically designed to compare the PK of oral melatonin in different ethnic populations were identified. Data presented in [Section 2.5.3.1.1 Absorption](#) indicate consistent values for PK parameters in subjects from a number of European countries and the USA, though it is probable that the subjects studied in each case were primarily Caucasian. The terminal T_{1/2} of ~ 44 minutes for a 10 µg *i.v.* dose of melatonin reported by [REDACTED] for 5 healthy subjects selected from a group of 22 men and women in the age range 30 – 63 years who are expected to be Japanese is comparable to the value of 45 minutes estimated for melatonin (administered *i.v.* or orally) in a systematic review of the clinical PK of melatonin ([REDACTED]) cited a study [REDACTED] that found Koreans to have significantly lower CYP1A2 activity than Swedes after controlling for CYP1A2 genotype, smoking habit, and oral contraceptive use. As this isoenzyme is primarily responsible for the metabolism of melatonin, this finding may have implications for the bioavailability of melatonin in this racial group.

2.5.3.1.6.4 Genotype

Limited data are available regarding the influence of genetic factors on the PK (and PD) of melatonin. [REDACTED] found the inhibitory effect of a large dose of caffeine on the metabolism of a 6 mg dose of IR melatonin ingested by 12 healthy younger men and women to be more pronounced in individuals with the CYP1A2*1F/*1F homozygote genotype (see [Section 2.5.3.1.8 Pharmacokinetic drug interactions affecting melatonin](#)).

[REDACTED] found that genotype for CYP1A2 (wild-type or with the g.-163C>A polymorphism) did not significantly affect the PK (AUC, C_{max}, T_{max} T_{1/2}) of a 6 mg dose of IR melatonin alone or in combinations with oral contraceptives in a study involving 31 healthy younger men and women (see [Section 2.5.3.1.8 Pharmacokinetic drug interactions affecting melatonin](#) for further review of this study).

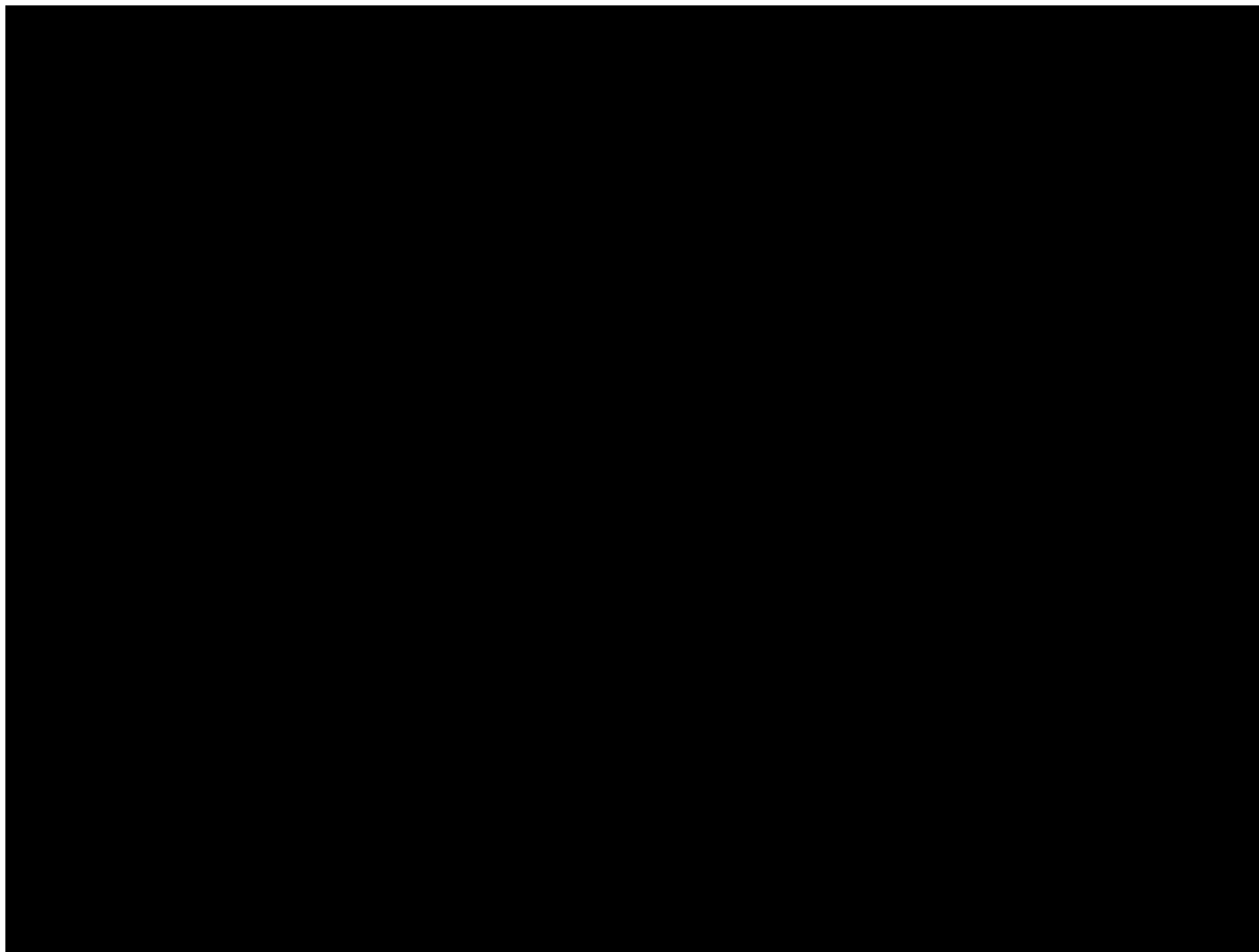
[REDACTED] suggested that loss of response to melatonin within a few weeks of treatment initiation, and its return after considerable dose reduction, seen in some patients given melatonin for sleep disorders may be due to slow metabolism of melatonin³⁰. Subsequently, [REDACTED] reported a single nucleotide polymorphism in the CYP1A2 gene to be associated with slow metabolism of melatonin, giving the potential for melatonin to accumulate with longer-term intake of larger doses. As the

[REDACTED]

Applicant's product is intended to be used periodically, with each treatment period having a recommended maximum length of 5 days, the issue of slow metabolism is not addressed in the proposed SmPC.

The possibility that exogenous melatonin may affect glucose homeostasis in bearers of a common variant of *MTNR1B* is discussed in [Section 2.5.3.2.3.1 Metabolic function](#) (Secondary pharmacodynamics and safety pharmacology).

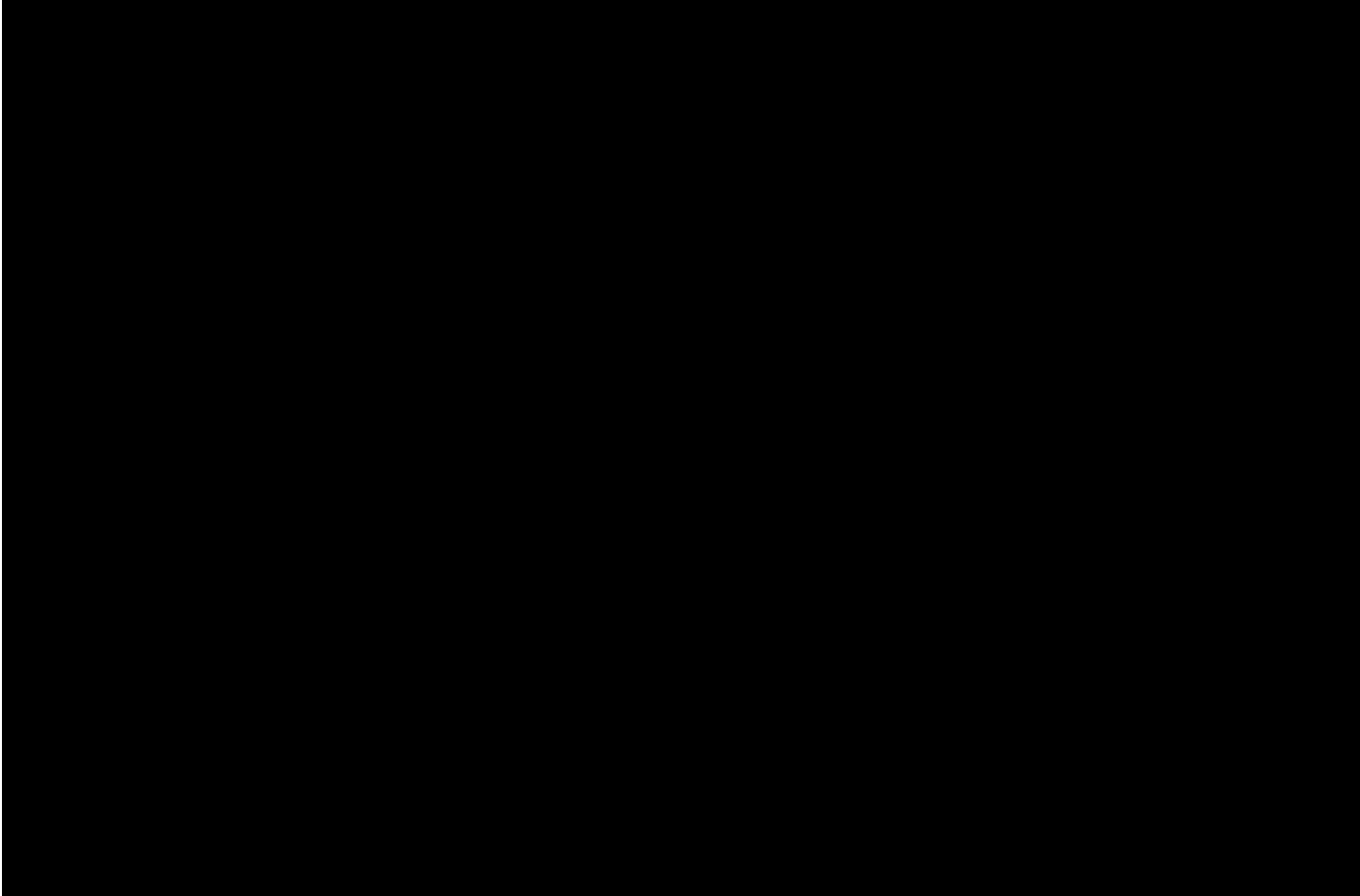
2.5.3.1.6.5 Hepatic impairment



In summary, limited data indicate that hepatic impairment can reduce the clearance of exogenous melatonin, though the data are inadequate to allow correlation. As there is no experience with use of the Applicant's product in patients with hepatic impairment it is not recommended for patients with severe hepatic impairment. There is insufficient data to permit alternative dosing recommendations for any degree of hepatic impairment. Relevant text is included in [Sections 4.2, 4.4 and 5.2 of the proposed SmPC](#).

2.5.3.1.6.6 Renal impairment





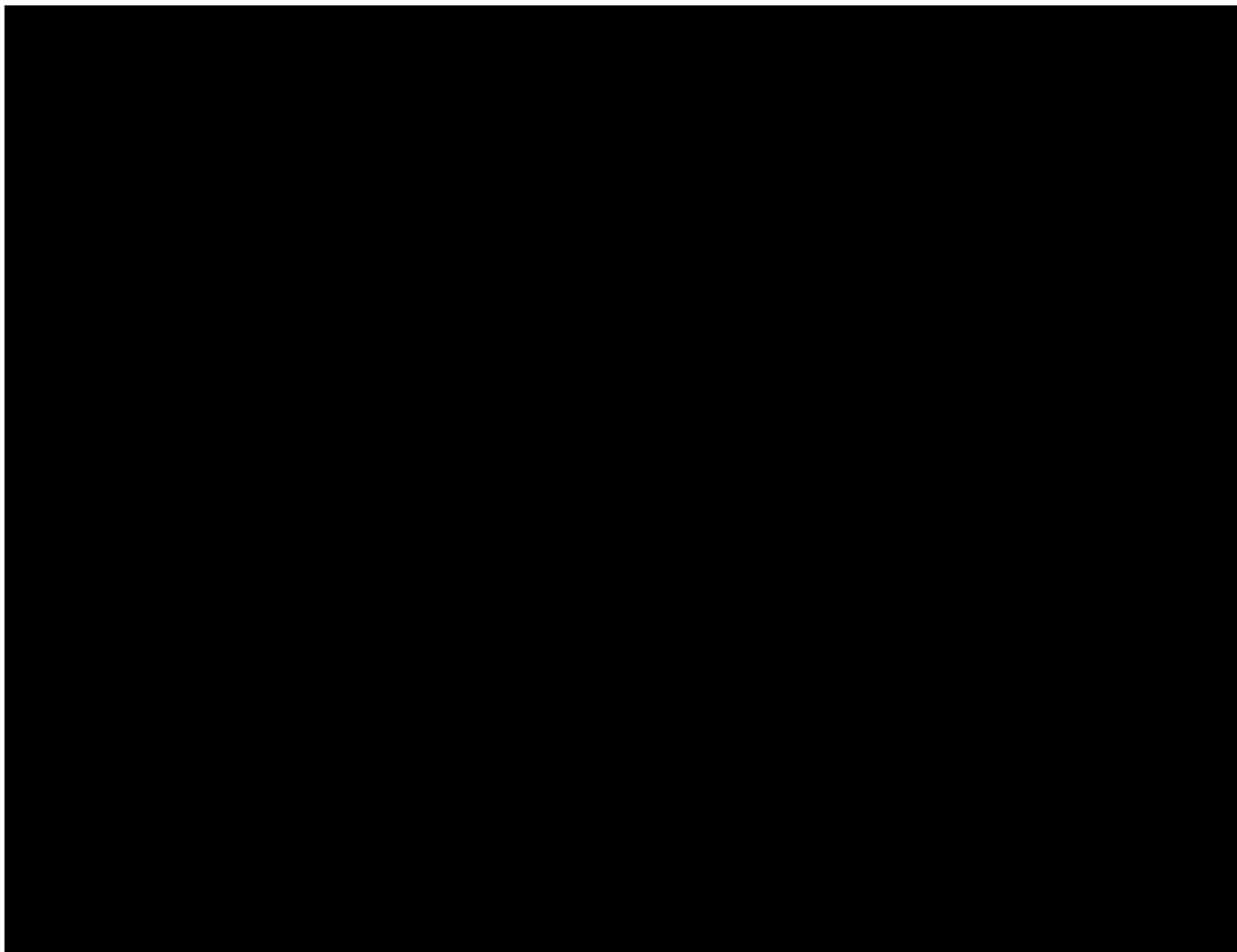
In summary, there are no data regarding the effect of renal impairment on the clearance of exogenous melatonin (parent molecule), though only a very small fraction (less than ~ 1%) of exogenous melatonin is excreted untransformed in urine. As melatonin metabolites are predominantly excreted in the urine, renal impairment can be expected to reduce their elimination. As there is only limited experience with use of the Applicant's product in patients with renal impairment it is not recommended for patients with severe renal impairment, and caution is recommended if melatonin is used by patients with renal impairment. There is insufficient data to permit alternative dosing recommendations for any degree of renal impairment. Relevant text is included in [Sections 4.2, 4.4 and 5.2 of the proposed SmPC](#).

2.5.3.1.7 Extrinsic factors affecting melatonin pharmacokinetics

Extrinsic factors (excluding drugs) that may influence the PK of oral melatonin addressed below are food, alcohol, and smoking. While the majority of persons taking melatonin are likely to be exposed to caffeine in the form of a beverage (coffee, cola, certain types of energy drinks), caffeine has been considered as a concomitant drug and is addressed in [Section 2.5.3.1.8 Pharmacokinetic drug interactions affecting melatonin](#).



2.5.3.1.7.1 Food (type and timing of meals)



In summary, although data for the effects of food on the PK of oral melatonin are limited (and do not address possible effects of food type), text noting that food can increase the absorption / plasma level of melatonin, but that it appears to have limited effect on T_{max}, is included in [Section 4.2](#) and/or [5.2 of the proposed SmPC](#). Text under the heading [Absorption in Section 5.2](#) also notes that the influence of food is not expected to affect the efficacy or safety of the product, however, it is recommended that food is not consumed approximately 2 before or 2 h after intake of melatonin. An interval between intake of food and melatonin is also considered warranted due to literature data indicating that intake of melatonin with carbohydrate-rich meals may impair blood glucose control for several hours (this issue is addressed in [Section 2.5.5.6.2 Glycaemic control](#)).

2.5.3.1.7.2 Alcohol

No literature studies examining the influence on alcohol consumption on the PK of oral melatonin were identified. The potential for alcohol to reduce the safety / efficacy of melatonin, and relevant information included under the *Posology* heading in [Section 4.2 of the proposed SmPC](#), are addressed in [Section 2.5.5.9.8 Food and alcohol](#).

2.5.3.1.7.3 Smoking

██████████ found the inhibitory effect of a large dose of caffeine on the metabolism of a 6 mg dose of IR melatonin to be more pronounced in smokers. ██████████ found that the AUC for a 25 mg oral dose of melatonin (administered at 09:30 hr) in 8 habitual smokers was 3-times greater when administered after 7 days abstinence from smoking compared to when administered prior to the pause in smoking (mean ($\pm$ SE) of 21.1 ± 7.38 vs. 7.3 ± 1.9 nmolL·h). Although data from specific, controlled studies are limited, cigarette smoke is recognised as a potent inducer of CYP1A2 ██████████ and thus can be expected to reduce the bioavailability of oral melatonin due to enhanced hepatic metabolism. Relevant information is included under the heading *Pharmacokinetic interactions* in [Section 4.5 of the proposed SmPC](#).

2.5.3.1.8 Pharmacokinetic drug interactions affecting melatonin

As noted in [Section 2.5.3.1.3 Metabolism](#), melatonin is metabolised mainly by CYP1A isoenzymes (primarily CYP1A2) of the cytochrome P450 system, giving the potential for PK interactions with other drugs for which CYP1A is an important route of metabolism. Text addressing the general potential for PK interactions with other drugs metabolised via CYP1A is included under the heading *Pharmacokinetic interactions* in [Section 4.5 of the proposed SmPC](#). Drugs that have been found to reduce metabolism of exogenous melatonin, resulting in a clinically significant increase in plasma melatonin level, include fluvoxamine, methoxypsoralens, and oestrogens, with caffeine having a less pronounced effect. Other drugs that, due to their route(s) of metabolism, can also be expected to reduce metabolism of melatonin, but for which no data for exogenous melatonin were identified in the literature, include quinolones (such as ciprofloxacin) and cimetidine. Drugs that, due to their capacity to induce isoenzymes of the cytochrome P450 system, can be expected to increase metabolism of melatonin and thus reduce plasma melatonin levels, but for which no data for exogenous melatonin were identified in the literature, include carbamazepine and rifampicin.

No PK interactions clearly involving drug transporters were identified in the literature

2.5.3.1.8.1 Fluvoxamine

██████████ reported that ingestion of 100 mg fluvoxamine at 16:00 hr by 8 healthy men (21 – 31 years) resulted in ~ 3-fold increases in the AUC and C_{max} for endogenous melatonin, and suggested inhibition of metabolism of melatonin to be the mechanism responsible. Likewise, ██████████ found ingestion of 50 mg fluvoxamine at 16:00 hr by 7 healthy subjects (3 women, 4 men; 21 – 44 years) to result in an ~ 2.8 fold increase in the AUC and C_{max} for endogenous melatonin; a second SSRI, citalopram, did not affect endogenous melatonin levels³³. It was proposed that fluvoxamine reduces the hepatic metabolism of melatonin via inhibition of cytochrome P450 enzyme(s) CYP1A2 or CYP2C19 or both. ██████████ found serum melatonin AUC be 17-times higher and C_{max} to be 12-times higher when 5 mg IR melatonin was ingested 3 h after ingestion of 50 mg fluvoxamine by 5 healthy male volunteers (34 – 55 years) who acted as their own controls. ██████████ noted that fluvoxamine is a potent inhibitor of primarily CYP1A2, but also of CYP2C19, CYP3A4 and CYP2D6, and did not discount effects of fluvoxamine on intestinal or hepatic transport processes.

Based on the above information, text has been included under the heading *Pharmacokinetic interactions* in Section 4.5 of the proposed SmPC stating that caution is indicated in patients treated with fluvoxamine, since it increases melatonin levels (17-fold higher AUC and 12-fold higher serum Cmax) by inhibiting its metabolism via the hepatic cytochrome P450 (CYP) isozymes CYP1A2 and CYP2C19; the combination should be avoided.

2.5.3.1.8.2 Methoxypsoralens (5- and 8-methoxypsoralen)

██████████ found oral 5-methoxypsoralen (5-MOP) to significantly increase plasma endogenous melatonin levels (evident from the second hour post-dosing) in 11 healthy subjects. Subsequently, ██████████ reported that a significant increase in plasma endogenous melatonin level occurred between 30 and 60 minutes after ingestion of 0.6 mg/kg bw 8-methoxypsoralen (8-MOP) by 15 patients admitted for routine psoralen plus UVA therapy; this increase was seen despite marked variation in the rate of 8-MOP absorption. Plasma 6-hydroxymelatonin sulphate concentration showed a concomitant decrease (already significant when first measured at 30 minutes), leading ██████████ to suggest that 8-MOP increases plasma endogenous melatonin level by inhibiting its metabolism. Recently, ██████████ confirmed that 5-MOP is a potent inhibitor of melatonin metabolism in human liver post-mitochondrial preparations. The lowest concentration studied (0.01 µM) caused partial inhibition of melatonin metabolism, while almost complete inhibition was seen at a concentration of 0.1 µM – markedly below the mean plasma concentration (1.75 µM) for 5-MOP following ingestion of a standard therapeutic dose. The inhibition was attributed to inhibition of 6-hydroxylation of melatonin, and ██████████ referred to an earlier study indicating that the Phase I metabolism of 5-MOP results in formation of a metabolite that interacts covalently with cytochrome P450 enzymes resulting in loss of activity. Based on the above information, text has been included under the heading *Pharmacokinetic interactions* in Section 4.5 of the proposed SmPC stating that caution is indicated in patients taking 5- or 8-methoxypsoralen (5- or 8-MOP), since this agent increases melatonin levels by inhibiting its metabolism.

2.5.3.1.8.3 Oestrogens

[REDACTED]

[REDACTED]

In summary, while a human *in vitro* study suggested a limited potential for ethinylestradiol-containing OCs to inhibit the metabolism of melatonin, a clinical study measured a significantly higher blood melatonin level when melatonin was ingested by women using OCs. It is unclear to what extent the size of the effect is influenced by the timing of melatonin intake in relation to the timing of intake of OCs. Post-marketing data for melatonin (see [Section 2.5.5.7 Post-marketing data](#)) have not suggested potential safety signals relating to concomitant intake of OCs (or HRT). Based on the above information, text has been included under the heading [Pharmacokinetic interactions in Section 4.5 of the proposed SmPC](#) stating that caution should be exercised in patients taking oestrogens (e.g. in the form of contraceptives or hormone replacement therapy), since oestrogens can increase melatonin level by inhibiting its metabolism, primarily via inhibition of CYP1A2.

2.5.3.1.8.4 Caffeine

[REDACTED] reported that caffeine (200 mg taken 1 h before, and 1 and 3 h after intake of 6 mg oral dose of IR melatonin in 12 healthy subjects (5 women, 7 men; 18 – 40 years) increased serum melatonin C_{max} and AUC (by 142% and 120%, respectively) and halved T_{max}. The inhibitory effect of caffeine was more pronounced in non-smokers and in individuals with the CYP1A2*1F/*1F homozygote genotype. Based on the latter finding (and the predominant role of CYP1A2 in the metabolism of melatonin), inhibition of CYP1A2 activity was suggested as a possible mechanism via which caffeine increased the bioavailability of melatonin. Due to the relatively high overall dose (600 mg) of caffeine taken both before and up to several hours after intake of melatonin, the data is not considered sufficiently applicable to warrant inclusion of a warning under the heading [Pharmacokinetic interactions in Section 4.5 of the proposed SmPC](#). As it is well known that caffeine is not conducive to sleep and should be avoided in the hours up to bedtime, the issue of caffeine intake is not addressed elsewhere in the proposed SmPC (e.g. under the heading [Posology in Section 4.2](#), as is the case for alcohol).

2.5.3.1.8.5 Other inhibitors of melatonin metabolism

Other drugs that are potent inhibitors of CYP1A2 include quinolones such as ciprofloxacin [REDACTED] and cimetidine, a potent inhibitor of several CYP isoenzymes [REDACTED]. Although no data on the effects of these drugs on the metabolism of typical therapeutic doses of melatonin were identified in the literature, they are named as examples of CYP1A2 inhibitors that may increase melatonin level in the text included under the heading [Pharmacokinetic interactions in Section 4.5 of the proposed SmPC](#).

2.5.3.1.8.6 Inducers of melatonin metabolism

Potent inducers of CYP1A2 include carbamazepine and rifampicin, with omeprazole also inducing this isoenzyme [REDACTED]. Although no data for the effects of these drugs on the metabolism of typical therapeutic doses of melatonin were identified in the literature, carbamazepine and rifampicin are named as examples of CYP1A2 inducers that may decrease melatonin level in text included under the heading [Pharmacokinetic interactions](#) in Section 4.5 of the proposed SmPC.

2.5.3.1.8.7 Drugs not considered to affect melatonin metabolism

Literature data for a number of other drugs suggest that they are unlikely to have a clinically significant PK interaction with exogenous melatonin.

Testosterone

[REDACTED] found 2 mg melatonin (probably IR) ingested at 18:00 hr for 2 months by 6 younger men (23 – 32 years) to have no effect on 24-h testosterone profile (AUC) (apart from the predicted phase-advancing effect on endogenous testosterone level). [REDACTED] found the plasma level of endogenous testosterone in 12 healthy adult men to be comparable during a control period and an 8-day period in which they ingested 100 mg IR melatonin at 16:00 hr. In addition, the plasma testosterone profile over the 6 days following *intra muscular* administration of 100 mg testosterone propionate on Day 8 was comparable during continued treatment with melatonin or placebo (see Figure 1 of the study report). The above findings are consistent with testosterone being metabolised primarily via CYP3A4 [REDACTED]. Based on the above information, testosterone is not addressed in relation to potential PK interactions in the proposed SmPC.

Imipramine and desipramine

[REDACTED] found that the tricyclic antidepressants imipramine and desipramine, at concentrations up to 20 µM, did not affect the metabolism of melatonin *in vitro* by human liver microsomes and recombinant human CYP isoenzymes. As imipramine and desipramine, plus the tricyclic antidepressants amitriptyline and nortriptyline, inhibit CYP2D6 and CYP2C19, and do not exhibit notable inhibition of other P450 isoenzymes [REDACTED] their potential for PK interaction with melatonin appears limited. Based on the above information, these drugs are not addressed in relation to potential PK interactions in the proposed SmPC.

Warfarin

The Cochrane review of melatonin for jet-lag [REDACTED], updated 2008) summarised 6 adverse drug reaction reports involving concomitant intake of melatonin and warfarin. As prothrombin time was increased in 3 of the reports and decreased in 3, a PK basis for an eventual interaction is considered unlikely. This is supported by the fact that the active enantiomer of warfarin (S-warfarin) is metabolised by CYP2C9 [REDACTED] and melatonin does not inhibit CYP2C9 *in vitro* [REDACTED] between melatonin and warfarin ([REDACTED]). The potential for a pharmacodynamic interaction between melatonin and warfarin is discussed in more detail in [Section 2.5.5.9.12.4 Other pharmacodynamic interactions](#), and a relevant text is included in Sections 4.5 of the proposed SmPC..

2.5.3.1.9 Conclusions on pharmacokinetics

The pharmacokinetics of exogenous melatonin has primarily been investigated in healthy men and women, though limited data are available for persons with hepatic impairment. The majority of studies, and the studies predominantly referred to in this application, have used various formulations that result in immediate release of melatonin, and are thus considered to provide data relevant to the Applicant's product.

Oral melatonin is efficiently (almost completely) absorbed from the gastrointestinal tract by first-order kinetics, though bioavailability (F) is low (~ 15%; range in individuals 1 to 56%) due primarily to extensive first-pass metabolism. A 3 – 6 mg dose of IR melatonin results in a peak in plasma melatonin concentration (T_{max}) ~ 50 minutes (normal range ~ 25 – 75 minutes) after ingestion. A 3 mg dose can be expected to result in a C_{max} of ~ 3400 pg/mL, which is ~ 60-times the peak nocturnal (endogenous) plasma melatonin C_{max}, though both values are subject to considerable inter-individual variation. Data correlating plasma concentrations of exogenous melatonin with efficacy or safety of melatonin for treatment of jet-lag are not available.

C_{max} and AUC (area under the concentration-time curve) are linear for oral melatonin doses in the range 0.1 to at least 5 mg, whereas T_{max} (and plasma elimination half-life (T_{1/2})) are constant.

Due to its small size and lipophilic, non-ionised nature, melatonin can be expected to rapidly move across cell membranes and into and out of tissue and organs. Data for levels of melatonin in different organs after ingestion of typical therapeutic doses of melatonin are not available, though exogenous melatonin has been shown to cross the blood-brain barrier and placenta, and it can be expected that it is excreted in milk. Plasma protein binding is in the range 50 – 60%; binding is primarily to albumin with limited binding to other plasma proteins. Melatonin is not strongly or extensively bound to plasma proteins, therefore significant effects of protein binding on melatonin PK (or drug interactions based on plasma protein binding) are not expected.

The cytochrome P450 system enzymes CYP1A1 and CYP1A2 are primarily responsible for metabolism of melatonin, with the liver the primary site of metabolism. The contribution of extra-hepatic metabolism is unclear but is minor. 6-hydroxymelatonin is the primary metabolite (~ 80 – 90% of melatonin metabolites recovered in the urine). Its formation is rapid, with plasma 6-hydroxymelatonin level rising within minutes of melatonin entering the systemic circulation. N-acetylserotonin, conjugated with glucuronide or sulphate, appears to be the primary minor metabolite. 5-methoxytryptamine, 2-hydroxymelatonin, and kynuramine derivatives are other more minor metabolites.

Excretion of melatonin metabolites, and a small quantity of melatonin (< 1%), occurs predominantly via the kidneys; faecal excretion of melatonin and its metabolites following ingestion of typical therapeutic doses of melatonin appears negligible. 6-hydroxymelatonin is excreted as its sulphate (~ 70%) and glucuronide (~ 30%) conjugates. T_{1/2} in healthy adults (including the elderly) is ~ 45 minutes (normal range ~ 30 – 60 minutes) and is essentially constant at oral doses up to 100 mg. T_{1/2} follows first-order (biphasic) elimination kinetics, and is independent of dose and route of administration.

As noted above, C_{max}, AUC and F show large inter-individual variability, even in quite homogeneous subjects (e.g. younger men or younger women in the same study). Variability in the extent of first-pass metabolism appears to be the primary explanation, though variability in the efficacy of absorption of melatonin may play a role.

Regarding intrinsic factors that can affect PK, the PK of oral IR melatonin the range 0.3 – 6 mg is generally comparable in younger and older adults, though the range of values for a given parameter tends to be greater in the elderly. There do not appear to be significant differences in the PK of oral IR melatonin in men and women, though C_{max}, AUC and F may be higher in women; no such tendency is evident for T_{1/2}. Data for the influence of race and genetic factors are limited, but are not considered to suggest any major concerns for efficacy or safety. Limited data indicate that hepatic impairment can reduce the clearance of exogenous melatonin, though the data are inadequate to allow correlation between degree of hepatic impairment and impact on clearance. Data regarding the effect of renal impairment on the clearance of exogenous melatonin are not available, though only a very small fraction (less than ~ 1%) of exogenous melatonin is excreted untransformed in urine. However as melatonin metabolites are predominantly excreted in the urine, renal impairment can be expected to reduce their elimination.

Regarding extrinsic factors that can affect PK, limited data suggest that ingestion of melatonin with food can increase absorption (C_{max} and AUC are increased) though with limited effect on T_{max}. Limited data also indicate that cigarette smoking reduces the bioavailability of oral melatonin, attributed to enhanced hepatic metabolism as a consequence of induction of CYP1A2 by agents in smoke.

As melatonin is metabolised mainly by CYP1A isoenzymes there is potential for PK interactions with other drugs for which CYP1A is an important route of metabolism. Drugs that have been found to reduce metabolism of exogenous melatonin – resulting in a clinically significant increase plasma melatonin level – include fluvoxamine, methoxypsoralens, and oestrogens, with caffeine having a lesser effect. Other drugs that, due to their route(s) of metabolism, can also be expected to reduce metabolism of melatonin, but for which no data for exogenous melatonin were identified, include quinolones (such as ciprofloxacin) and cimetidine. Drugs that, due to their capacity to induce cytochrome P450 isoenzymes, can be expected to increase metabolism of melatonin – and thus increase plasma melatonin level – but for which no data for exogenous melatonin were identified, include carbamazepine and rifampicin. No PK interactions clearly involving drug transporters were identified.

2.5.3.2 Pharmacodynamics

The following is a brief background and overview of the pharmacodynamics of endogenous melatonin and the pharmacology of exogenous melatonin. The published literature on these topics is extensive, though aspects of both remain unclear.

Melatonin is primarily secreted by the pineal gland. It is also synthesised by the retina and in other parts of the body (notably leukocytes and the intestinal mucosa). Pineal production is believed to be primarily responsible for plasma melatonin level. Pineal melatonin synthesis is modulated (via the SCN) by light transduced by the retina, with light of a given intensity suppressing synthesis. Consequently, plasma melatonin levels start to rise in the early evening, peaks in the early morning, and by around dawn has declined to the daytime nadir [redacted]. This rhythm typically has a periodicity of slightly longer than 24 hours, however daily exposure to light in the morning (and the subsequent hours of wakefulness) entrain the rhythm to 24 hours, as Melatonin secretion is inhibited by light and regulated by the circadian clock located in the hypothalamic suprachiasmatic nuclei. At the onset of darkness, reduced retinal input leads to the disinhibition of enzymes responsible for melatonin synthesis. This increased nighttime synthesis results in peak nocturnal plasma concentrations of about 80 to 120 pg/mL between 2 and 4 am, levels

decrease until daylight onset, with low (10–20 pg/mL) concentrations being observed during the daytime [REDACTED]

Night-time (measured once between 23:00 and 01:00 hr) plasma / serum melatonin level is low during the first 6 months of life (27 ± 5 pg/mL), increases to a peak at 1 – 3 years (326 ± 42 pg/mL), while at age 15 – 20 years is considerably lower (63 ± 9 pg/mL) and in the following decades declines moderately until old age (29 ± 6 pg/mL) [REDACTED]

[REDACTED] A marked decline in endogenous (essentially night-time) melatonin secretion occurs around the time of onset (~ 9 – 10 years) of puberty, and it has been suggested that the high (nocturnal) melatonin level prior to this age may inhibit puberty, though the pre-pubertal decline could instead be a consequence of, rather than an initiator / mediator of, puberty [REDACTED] This issue is discussed in detail in [Section 2.5.3.2.3.5 Sexual development](#) (Secondary pharmacodynamics and safety pharmacology).

The cause of the decline in nocturnal plasma melatonin level (and the advance in the onset of secretion and peak level) seen in older age are uncertain, but are attributed to a combination of endogenous and exogenous factors³⁵. The contribution of changes in the circadian system, such as altered melatonin secretion profile and amplitude, to age-related impairment of sleep (e.g. increased sleep onset latency (SOL), more frequent night awakenings, awakening too early in the morning) provides a rationale for testing melatonin for the treatment of insomnia in older persons ([REDACTED]). A prolonged-release melatonin product was Centrally Authorised for such an indication in 2007³⁶. There are no indications that the efficacy and safety of melatonin (including IR melatonin for jet-lag) are significantly affected by older age. These issues are addressed in [Section 2.5.3.2.2 Primary pharmacokinetics](#) and [Section 2.5.5.9.1 Elderly](#) (Safety in special groups and situations).

The time at which melatonin starts to rise under dim light conditions is termed the 'dim light melatonin onset' (DLMO)³⁷. In adults with a regular sleep-wake rhythm, DLMO usually occurs about 2 hours before sleep onset ([REDACTED]). Exposure to exogenous IR melatonin at least a couple of hours prior to DLMO advances DLMO, while exposure to exogenous melatonin at least several hours after DLMO delays the subsequent DLMO [REDACTED]. Studies of the effects of administration of melatonin before or after DLMO in persons with a synchronised circadian rhythm can provide information on the functions of melatonin, and there is good evidence that endogenous melatonin affects the circadian rhythmicity of sleep, core body temperature, other hormones such as cortisol, and of its own secretion [REDACTED]. This capacity of exogenous melatonin to modulate circadian rhythmicity provides the rationale for treating circadian rhythm disturbances by administering melatonin at a time of day that aids re-entrainment.

Jet-lag is a disorder in which voluntary human activity temporarily desynchronises circadian rhythmicity (including the melatonin synthesis profile) and the normal (at travel destination) sleep-wake cycle. In essence, melatonin level is elevated at an inappropriate time of day, resulting in inappropriately-timed effects on body functions. After flight in eastern direction DLMO and corresponding sleep-wake rhythm are delayed relative to the new time zone, and adjustment requires DLMO and sleep-wake rhythm to advance, with

[REDACTED]

the opposite applying to flight in western direction. While circadian rhythmicity will gradually re-synchronise this can take several days depending on the number of time zones crossed and the direction of travel³⁸. Field studies of jet-lag, and laboratory studies of simulated jet-lag, have demonstrated that exogenous melatonin can reduce the duration and severity of jet-lag. The effect does not appear to be mediated solely by reduced disturbance of sleep, but rather by improvement in global symptoms of jet-lag that include factors such as daytime tiredness and fatigue, mild cognitive impairment, irritability, and gastrointestinal disturbances.

The following sections addresses the mechanisms of action, primary pharmacodynamics, and secondary pharmacodynamics and safety pharmacology of exogenous melatonin, with reference to endogenous melatonin where appropriate (notably in relation to mechanisms of actions). The Applicant has attempted to select representative studies from the large number of studies in the literature.

2.5.3.2.1 Mechanism of action

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine synthesised and secreted by the pineal gland in the human brain. It is also synthesised in the retina, thymus, bone marrow, respiratory epithelium, skin, intestine, and in other sites, though extrapineal melatonin generally does not gain access to the systemic circulation [REDACTED]

[REDACTED] Two functional groups (decisive for its receptor binding) impart amphiphilicity, giving melatonin the capacity to enter all cell compartments and body fluids.

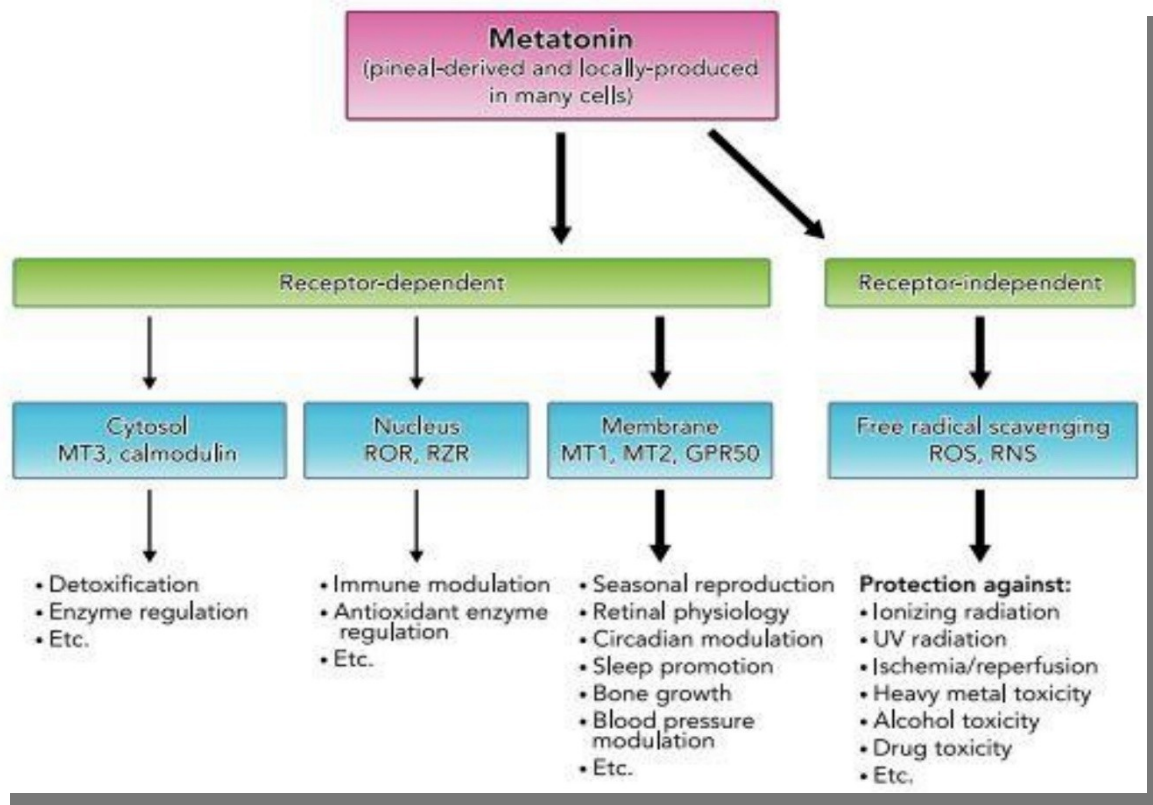
Consequently, melatonin secreted by the pineal gland passes freely through membranes and distributes in all body compartments [REDACTED]

[REDACTED] and it can be expected that exogenous melatonin behaves in the same way. Exogenous melatonin has been shown to cross the blood brain barrier ([REDACTED]) allowing it to bind to melatonin receptors in the brain.

Melatonin exerts its physiological actions primarily³⁹ through the G-protein-coupled receptors MT1 and MT2, although it may also work through the cytosol-located MT3 receptor, directly in the nucleus through nuclear receptors or through a receptor-independent pathway [REDACTED] see also [figure 2.5.3.2.1-1](#) taken from [REDACTED] below. These receptors are classified as unique subtypes based on their molecular structure and chromosomal localisation. The binding affinity (expressed as IC50) of melatonin to MT1 is 0.085 nM and to MT2 0.263 nM. These receptors are located in the hypothalamic SCN, the biological 'clock' that regulates circadian rhythms, including the secretion of pineal melatonin itself. MT1 and MT2 are also expressed in the cerebellum, cortex, hippocampus, and hypothalamus, and in cerebral arteries. Another melatonin binding site, MT3, has low affinity to melatonin (10 nM). It is widely distributed in the body and modulates calcium and calmodulin activity [REDACTED]

Figure 2.5.3.2.1-1

The two main melatonin physiological pathways in humans. The receptor-dependent and receptor-independent pathways are shown with their relevant families of receptors and their associated pleiotropic physiological effects (Figure taken from review by [REDACTED]).



The MT1 and MT2 melatonin receptor subtypes are complementary in their actions and, to some extent, mutually substitute for each other. Both receptors involve signaling through inhibition of cyclic adenosine monophosphate (cAMP) formation and protein kinase A activity, and effects on phospholipase A2 and C, calcium and potassium channels. The high density of melatonin receptors in the SCN suggests that melatonin affects sleep and the sleep-wake cycle by acting on these receptors. Melatonin inhibits SCN firing via MT1 receptors, and activation of MT2 receptors mediates melatonin's phase-shifting effects. Melatonin may also alter the functions of the GABA-A-benzodiazepine receptor complex. These effects, which are presumably linked to the activation of GABAergic mechanisms in the SCN, are the putative mechanisms by which melatonin contributes to the circadian timing of the sleep-wake cycle ([REDACTED]).

The central nervous system, and specifically the SCN, are primarily responsible for control of diurnal rhythms. The SCN 'clock' is entrained to a 24-h day by the natural light-dark cycle transduced via retinal light input (bright light suppresses melatonin synthesis). The chronobiotic effect of melatonin is due to its direct influence on the electrical and metabolic activity of the SCN, and on the expression of its clock genes and those of the pars

tuberalis. Circadian regulation is also modulated by the interactions of neurotransmitter functions, for example the highest concentration of serotonin in the CNS is in the SCN, and its turnover exhibits marked circadian and seasonal rhythm ([REDACTED] [REDACTED])

Thus, the most significant regulatory factor in the production of pineal melatonin is the daily alternation of light and darkness. Melatonin is secreted mainly at night with maximum plasma levels occurring between 02:00 and 04:00 hr. The retina detects ambient light intensity and conveys this information to the brain. The circadian pacemaker in the SCN drives melatonin synthesis and secretion from the pineal gland. In humans, the circadian rhythm of pineal melatonin release is highly synchronised with the habitual hours of sleep, and the daily onset of melatonin secretion is well correlated with the subsequent onset of nocturnal sleepiness. The peak in melatonin production also coincides with the nocturnal trough in body temperature, and the normal nighttime decrease of the body temperature rhythm is partially mediated by the nocturnal rise in endogenous melatonin production. Melatonin has both phase-shifting effects (changing the timing of the biological clock), and direct sleep-facilitating effects. As melatonin receptors are widespread in the brain, the hypnotic effect of larger doses of exogenous melatonin may be related to actions at sites other than the SCN. Brain imaging studies in awake subjects have revealed that melatonin modulates brain activity pattern to one resembling that of actual sleep ([REDACTED] [REDACTED])

An increase in plasma cyclic guanosine monophosphate (cGMP) level after melatonin intake suggests a correlation between an increase cGMP level and the sleep-promoting effect of melatonin ([REDACTED])

2.5.3.2.2 Primary pharmacodynamics

Based on the mechanisms of action of melatonin discussed in the previous section, exogenous melatonin can be expected to limit and treat symptoms of jet-lag by hastening the re-entrainment of circadian rhythmicity, including the rhythmicity of endogenous melatonin secretion, and via a direct sleep-inducing / maintenance action. Oral melatonin at typical pharmacological doses shifts circadian rhythms in humans according to a phase-response curve that is nearly opposite the phase-response curves for light exposure. Melatonin delays circadian rhythmicity when administered after dim light melatonin onset (DLMO) and advances it when administered before DLMO⁴⁰ ([REDACTED] [REDACTED])

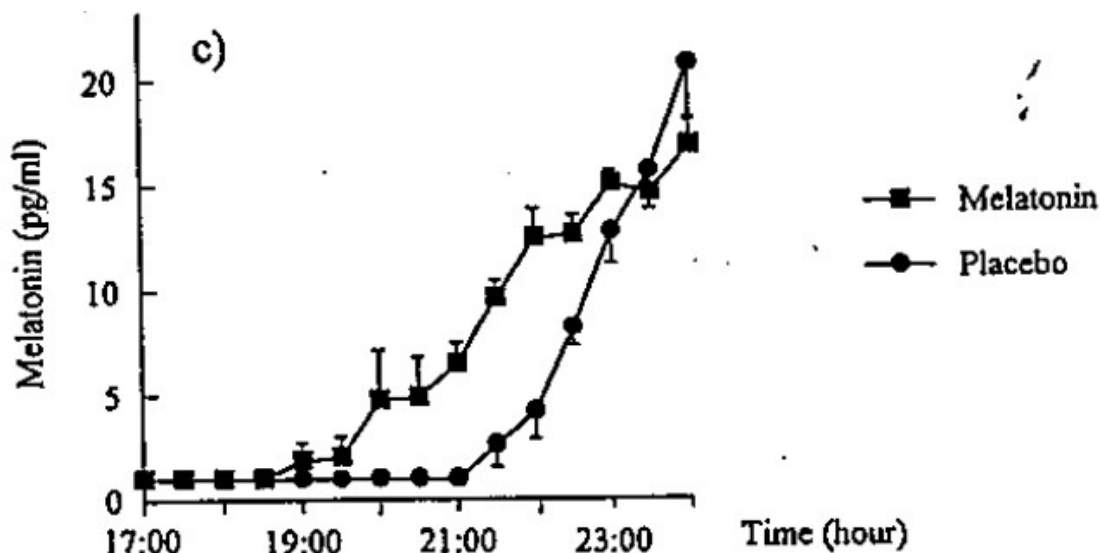
2.5.3.2.2.1 Effects on endogenous melatonin rhythmicity

A crossover RCT [REDACTED] examining the association between reduction in core body temperature and the acute phase-shifting effects of melatonin found that 5 mg oral IR melatonin administered to 8 young men (23 – 28 years) at 17:00 hr significantly advanced DLMO⁴¹ (mean ($\pm$ SD) 1.14 $\pm$ 0.49 h) the following day (see [Figure 2.5.3.2.2.1-1](#)). The degree of phase-shift was correlated with the degree of temperature decrease (this study is discussed in more detail in [Section 2.5.3.2.2.4 Effect on body temperature](#)).

Figure 2.5.3.2.2.1-1



Time course of endogenous melatonin secretion as assessed by saliva melatonin concentration during the evening after administration of 5 mg melatonin at 17:00 hr the previous day (Figure 1c of the study report of [REDACTED])



A RCT of melatonin for jet-lag [REDACTED] in which 10 women and 7 men (29 – 68 years) ingested 5 mg melatonin (probably IR) or placebo at bedtime for 2 days pre-flight, on the day of departure, and for 4 days post-flight (eastward over 8 time zones), found re-synchronisation of melatonin rhythm (determined via measurement of the primary urinary melatonin metabolite at the end of the treatment) to be more rapid in subjects receiving melatonin.

A second RCT of melatonin for jet-lag [REDACTED] in which 26 men and 10 women (22 – 37 years) ingested 5 mg melatonin (probably IR) or placebo at bedtime for 7 days following eastward flights crossing 6 – 7, 8 – 9, or 10 – 11 time zones did not find a clear effect of melatonin on the rate of re-synchronisation of endogenous melatonin rhythm (determined via measurement of salivary melatonin and the primary urinary melatonin metabolite at the end of the 5-day treatment phase).

An open study of melatonin for jet-lag [REDACTED] found intake of 3 mg melatonin at bedtime (23:00 hr) on Days 2 – 4 after an 8-h eastward flight to result in more rapid resynchronisation of endogenous melatonin rhythm than when the same subjects had not taken melatonin on a previous, comparable flight (daily shift in re-entrainment 76 minutes with melatonin vs. 31 minutes without).

2.5.3.2.2.2 Effects on cortisol rhythmicity

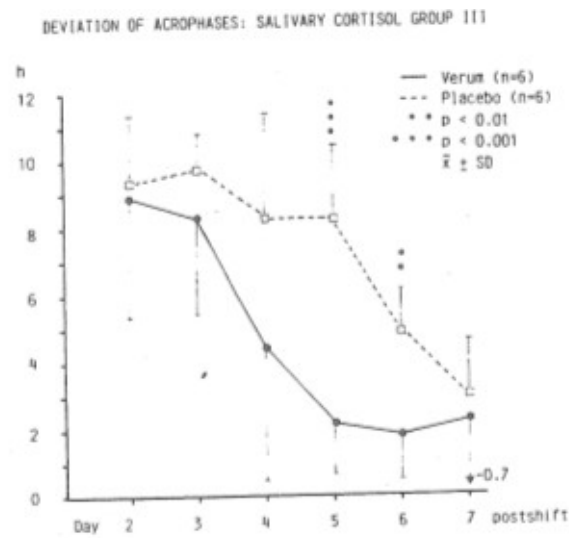
Administration of melatonin during the day has been found to advance the phase but not to have a significant effect on the amplitude of diurnal plasma cortisol profile ([REDACTED])

The RCT of melatonin for jet-lag of [REDACTED] referred to in the previous section found ingestion of 5 mg melatonin at bedtime to result in more rapid re-synchronisation of cortisol rhythm (determined via urinary free cortisol).

Likewise, the RCT of melatonin for jet-lag of [REDACTED] referred to in the previous section found ingestion of 5 mg melatonin at bedtime to result in faster re-entrainment of the acrophase of salivary cortisol in all melatonin / flight duration groups compared to placebo, with the size of the effect increasing with the number of time zones crossed (*Figure 2.5.3.2.2-1* presents data for the subjects crossing 10 – 11 time zones).

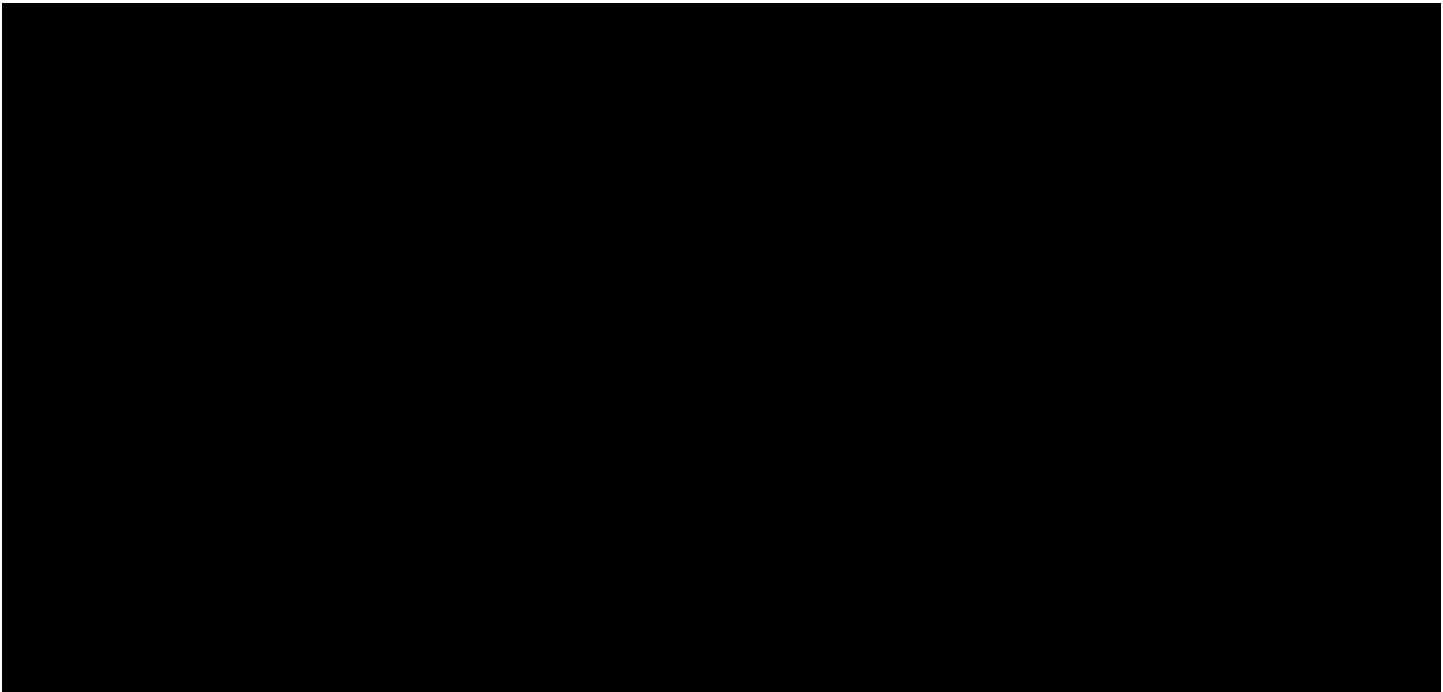
Figure 2.5.3.2.2-1

Effect of 5 mg oral melatonin on the mean post-shift acrophase of salivary cortisol relative to the baseline (pre-shift) acrophase following an eastward flight over 10 – 11 time zone
 (Figure 1 of the study report of [REDACTED])

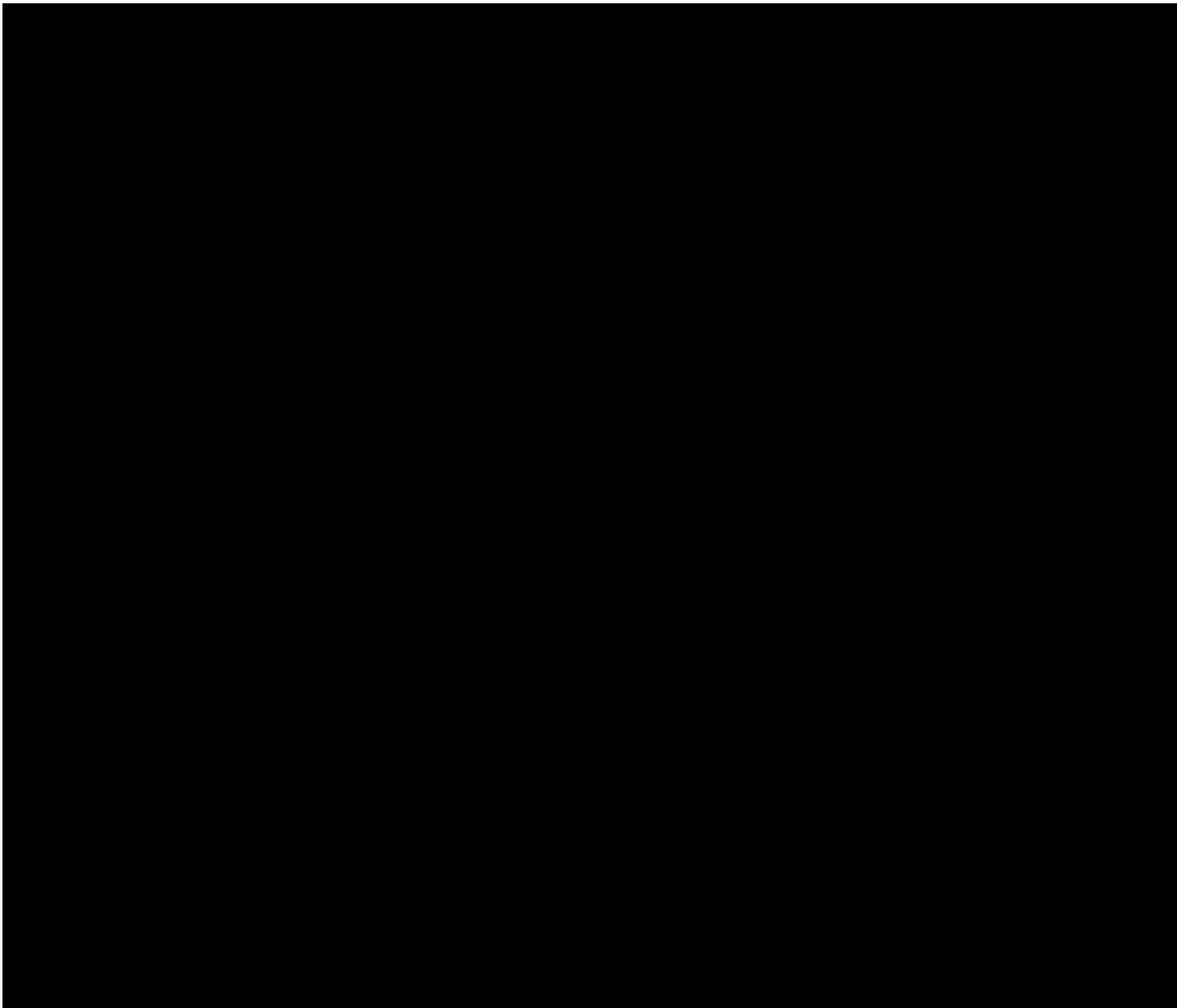


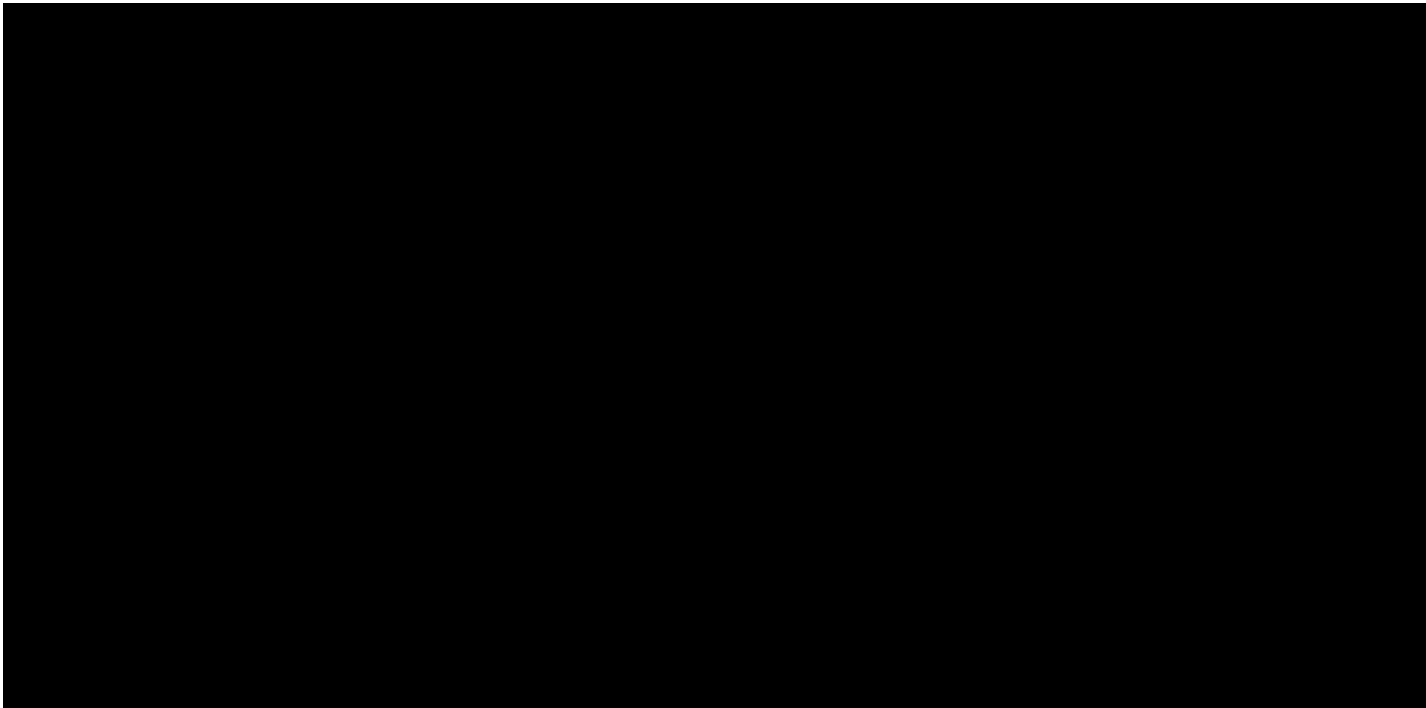
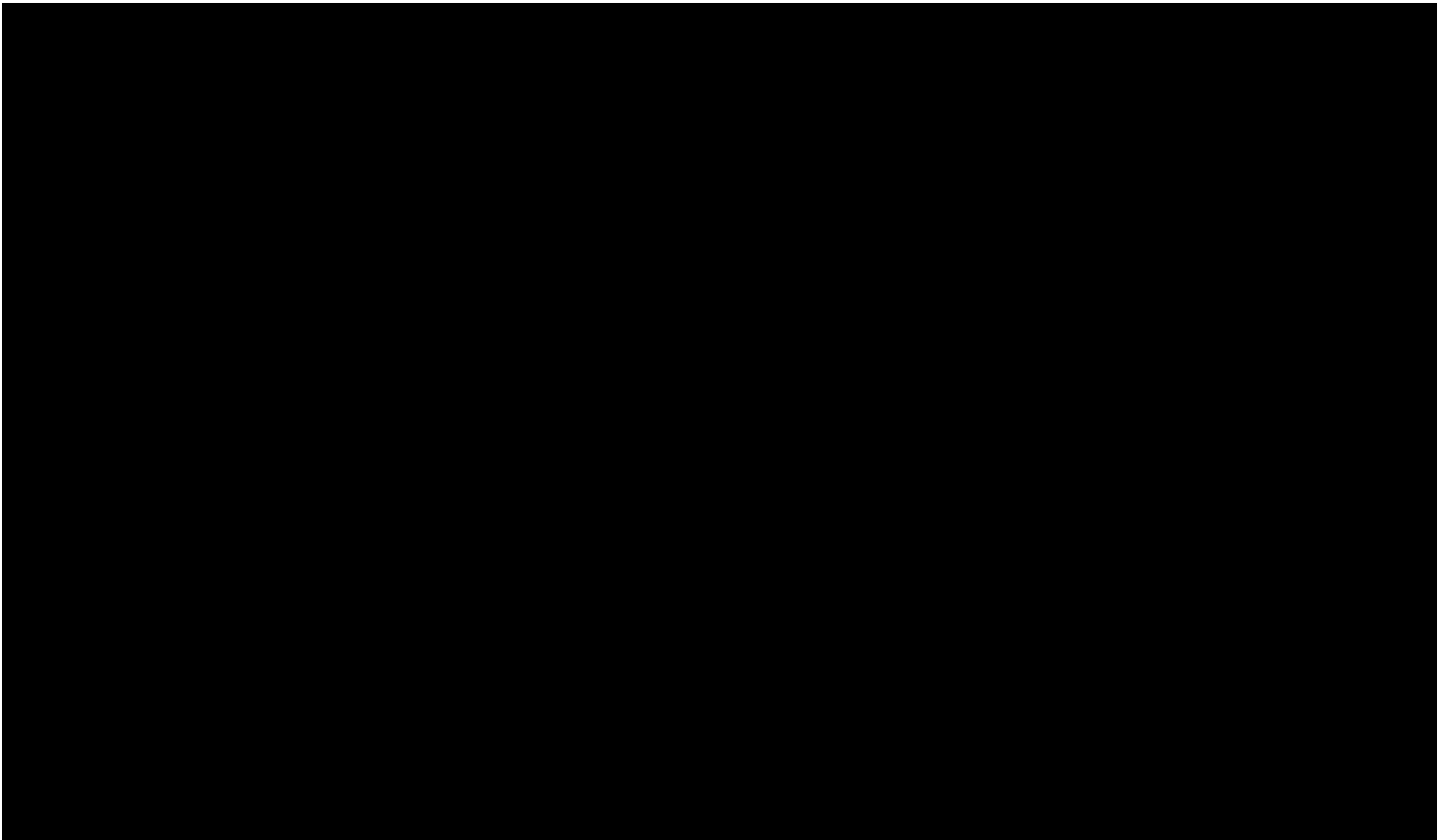
A third jet-lag study ([REDACTED]) found ingestion of 5 mg melatonin daily before, during, and after an eastward flight over 7 time zones to hasten resynchronization of cortisol rhythm during the 4 days post-flight.

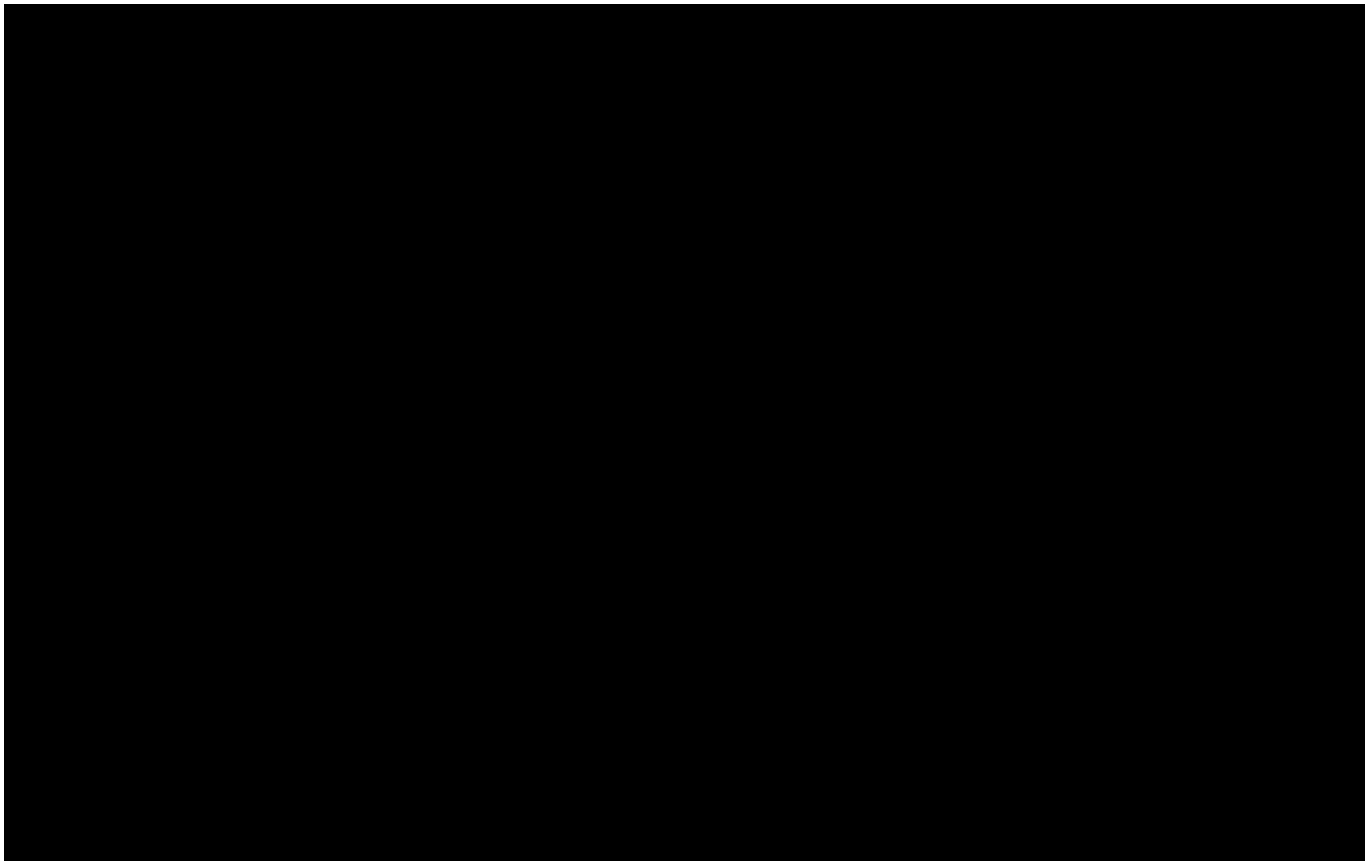
2.5.3.2.2.3 Sleep-inducing / maintenance effects



[REDACTED]







In summary, oral melatonin has been found to reduce sleep onset latency, with some evidence that it improves sleep quality and sleep architecture. The sleep-inducing effect is evident regardless of the time of administration, though – not unexpectedly – there is a degree of attenuation with administration around DLMO. The effects of oral melatonin on sleep may be mediated by a reduction in core body temperature, and possibly also by potentiation of the effects of gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter of the CNS⁴⁴, via direct interaction with GABA receptors.

The capacity of oral melatonin to improve sleep parameters in jet-lag is addressed in **Section 2.5.4.1 Efficacy of melatonin for treatment of jet-lag**. In brief, 5 of 7 studies⁴⁵ found a significant improvement (1 a strong tendency) in sleep quality, and 3 of 5 studies a significant improvement in sleep onset latency and daytime tiredness. A jet-lag study ([redacted]) examining 0.5 and 5 mg doses of oral IR melatonin reported a dose-dependent reduction in sleep onset latency and the 'ease' with which subjects fell asleep.

2.5.3.2.2.4 Effect on body temperature

The circadian rhythm of core body temperature (CBT) in humans is characterised by maximum values during the day and minimum values during the night, and is normally

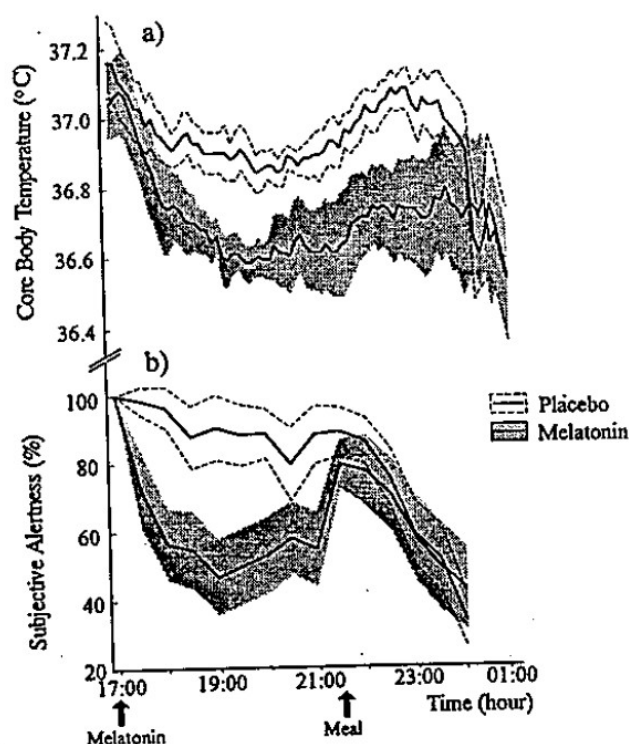


coupled with the sleep-wake cycle. For example, in young, healthy women, serum melatonin remained at a low and constant level between 08:00 and 20:00 hr while body temperature gradually increased to peak at 18:20 hr, after which it decline and serum melatonin level increased, with a strong inverse correlation (). The latter changes preceded the onset of sleep by ~ 3 h. Melatonin reinforces the nocturnal decrease of CBT, an event which facilitates sleep propensity. Melatonin receptors have been identified in peripheral vasculature, such that the nocturnal decrease CBT may be at least partly due to peripheral vasodilation (and subsequent heat loss) mediated by melatonin receptor stimulation (). The RCT of () summarised in the previous section, which found single oral doses of 0.1 – 10 mg IR melatonin administered at 11:45 hr to 22 young men to shorten sleep onset and enhance sleep duration, also found melatonin to decrease oral temperature in a significant, dose-dependent manner (see [Table 1](#) and [2 of the study report](#)).

In a cross-over RCT () designed to examine the association between the acute phase-shifting effects of melatonin and reduction of CBT, 5 mg IR melatonin or placebo was administered to 8 healthy men (23 – 28 years). Each phase of the study was performed over 5 days. Days 1 and 2 served to establish normal sleep-wake cycle, on Day 3 subjects received melatonin or placebo at 17:00 hr. On Day 3 and Day 4 subjective drowsy-alert scores were rated, while sleep quality was rated for the nights of Days 2 – 4. Rectal temperature was measured continuously from 08:00 hr on Day 2 until 08:00 hr on Day 5. Melatonin induced an acute, transient reduction in CBT between 17:00 and 24:00 hr, with ANOVA identifying a significant treatment effect on temperature between 18:12 and 20:30 hr, with a mean ($\pm$ SD) fall in temperature of 0.26 ± 0.19 °C (see [Figure 2.5.3.2.2.4-1](#)). A significant treatment effect on alertness between 17:00 and 21:00 hr was also identified, with mean ($\pm$ SD) reduction of $31.1 \pm 1.1\%$.

Figure 2.5.3.2.2.4-1

Time course of suppression of core body temperature and subjective alertness following ingestion of 5 mg melatonin (Figure 1a and b of the study report of [REDACTED])



A crossover RCT [REDACTED] studied the hypothermic effect of 0.1, 0.5, 1.0 or 5.0 mg IR melatonin on CBT in 21 men and 11 women (healthy; aged 18 – 38 years). Following 8 h bed rest (08:00 – 16:00 hr) melatonin was ingested at 16:00 hr. CBT was measured during the 8 h prior to intake of melatonin and for 4 h afterwards. Tmax for blood melatonin did not differ significantly between the 4 melatonin doses. Fisher's PSD analysis indicated that, in general, CBT was reduced in a significant, dose-dependent manner by melatonin: mean maximum decline in CBT was 0.08, 0.15, 0.20 and 0.25 °C for the 0.1, 0.5, 1.0 and 5.0 mg doses, respectively. As CBT did not decline in some subjects receiving the the 2 lowest doses, the authors suggested that to improve sleep onset and maintenance melatonin doses between 1.0 and 5.0 mg should be used.

A crossover RCT [REDACTED] in which 6 young men ingested 3 or 9 mg IR melatonin or placebo at 09:30 hr found both doses to significantly decrease CBT, with the greatest effect between 11:30 and 12:00 hr; the effect was not dose-dependent (see Figure 1 of the study report). The study also found that melatonin induced a significant reduction of sleep latency (see [Section 2.5.3.2.2.3 Sleep-inducing / maintenance effects](#)), and it was suggested that exogenous melatonin exerts its circadian phase-shifting effect via a transient hypothermic action.

2.5.3.2.3 Secondary pharmacodynamics and safety pharmacology

In addition to its role as a chronobiotic, including its capacity to hasten re-entrainment of circadian rhythmicity following rapid transmeridian travel (i.e. its proposed use in the treatment of jet-lag), *exogenous* melatonin has been found (or been suspected) to affect the nature of a number of physiological processes. The potential for exogenous melatonin

to adversely affect the trio of systems in the core safety battery (i.e. nervous-, respiratory, and cardiovascular systems) is limited, as reflected in the fact that such effects have generally not been raised as concerns in reviews addressing the safety of melatonin (see [Section 2.5.5.5.2 Reviews addressing melatonin safety](#)). The following sections address secondary pharmacodynamic actions of exogenous melatonin that are considered potential safety concerns, namely effects on metabolic function (specifically glycaemic control), cardiovascular function, immune system function, reproductive function, sexual development, and analgesic effect.

2.5.3.2.3.1 Metabolic function

Endogenous melatonin plays a role in the timing and regulation of metabolic functions that include energy metabolism, insulin secretion, and glucose homeostasis. Distribution of energy metabolism over the day is modulated by the profile (level) of endogenous melatonin. Melatonin deficiency causes increased hepatic gluconeogenesis and hepatic insulin resistance during the active phase of the rest / activity cycle, which is largely detrimental because both metabolic processes should peak during the fasting period and not during feeding or soon after. Human data suggest that exposure to light during the night (during shift-work or as 'pollution') reduces melatonin synthesis and impairs metabolic homeostasis (). The following sections summarise the effect of exogenous melatonin on metabolic function, specifically glycaemic control.

Effects of melatonin on glycaemic control in healthy subjects

() found that ingestion of 6 or 12 mg melatonin (formulation unstated) by 18 healthy younger men (27 – 36 years) at 07:30 hr did not affect basal- or angiotensin II-stimulated plasma oxytocin concentration, but that the oxytocin response to insulin-induced hypoglycaemia in an insulin tolerance test (ITT) started 30 minutes after intake of melatonin was significantly reduced (~ 38%). The change in plasma glucose during the ITT was comparable in the control and melatonin groups.

Two studies have examined the effects of melatonin on post-prandial glycaemic control via an OGGT commencing 15 – 45 minutes after intake of melatonin, and their findings are considered particularly relevant to intake of melatonin close to meals.

() found the AUC for serum glucose (+14%) and serum C-peptide (+26%), but not serum insulin (+12%), to be significantly increased in 13 healthy post-menopausal women (52 – 61 years) who acted as their own controls when an OGGT (75 g) was performed starting 45 minutes after ingestion of 1 mg IR melatonin at 08:00 hr (see Figure 1 of the study report). In a separate experiment in which 9 women of similar status underwent a frequently-sampled intravenous glucose tolerance test starting 45 minutes after ingestion of 1 mg IR melatonin at 08:30 hr, a significant 26% reduction in insulin sensitivity was observed; the alteration induced by melatonin was inversely related to insulin sensitivity on the control day. The above effects of melatonin were not influenced by the age or body mass index of the subjects or use of HRT.

() examined the effect on glucose tolerance of 5 mg IR melatonin ingested 15 minutes before an OGGT (75 g) starting at 09:00 hr or 21:00 hr in 21 healthy young women (24 ± (SD) 6 years) who acted as their own controls. Following intake of melatonin in the morning, the AUC for plasma glucose (+186%) and peak plasma glucose (+21%) were significantly increased, as was also the case following intake of melatonin in the evening (+54% and +27% respectively), compared to placebo. The AUC for plasma insulin was unchanged on intake of melatonin in the morning, but significantly increased (+45%) on intake in the evening (see Figure 1 of the study report). As absolute values, the

AUCs for plasma glucose and insulin were greater in the evening. Together, the data were considered to indicate that melatonin decreased insulin sensitivity (especially in the evening) and resulted in insufficient β -cell compensation (especially in the morning). In summarising their results, [REDACTED] noted *“the present results suggest that one may need to consider the proximity of melatonin administration to meal timing, particularly in those at risk for glucose intolerance or T2D [Type 2 diabetes], the optimum time should be at least 2 hours after the last meal to allow partial recovery of normal plasma glucose values before melatonin administration and therefore to avoid the associated impaired glucose tolerance. ... data suggest that duration between a meal and melatonin administration may need to be even longer in patients with impaired glucose tolerance and T2D.”*

Several studies have reported data for fasting (or at least not post-prandial) blood-glucose and lipids following longer-term intake of melatonin. [REDACTED] found intake of 10 mg melatonin (probably IR) 1 h (at ~ 22:00 hr) before sleep for 28 days to have no effect on blood- glucose, triglycerides, cholesterol fractions, or on any other routine biochemical tests (all probably measured fasting at ~ 10:00 hr) in 30 healthy young men (29 ± 1 year). Likewise, [REDACTED] found ingestion of 3 mg melatonin (probably IR) 30 minutes before bedtime for 6 months to have no effect on blood- glucose or lipids, or on any other routine biochemical test (all probably measured fasting) in 22 subjects (60.1 ± 9.5 years; 16 women) with insomnia (20 taking a benzodiazepine).

Effects of melatonin on glycaemic control in diabetics

No studies addressing potential effects of melatonin taken shortly (within 1 – 2 h) of a meal on post-prandial glycaemic control in diabetics were identified in the literature. Several studies have addressed the effect of melatonin on long-term blood- glucose and lipid control in diabetics.

[REDACTED]

In summary, ingestion of 5 mg melatonin 15 minutes before an OGGT performed in the evening increased plasma glucose level (Cmax, AUC) in healthy women; a comparable study of persons with glucose intolerance or diabetes was not identified. Longer-term (at least 3 weeks) ingestion (typically close to bedtime) of doses of melatonin comparable to or greater than the recommended doses for the Applicant's product did not adversely affect fasting blood- glucose or lipids in healthy persons, nor on fasting blood- glucose, HbA1c, or lipids in Type 2 diabetics; HbA1c was, in fact, improved.

Safety issues and adverse effects relating to glycaemic control during melatonin treatment are addressed in [Section 2.5.5.6.2 Adverse effects on glycaemic control](#), which also summarises safety information relating to glycaemic control included in the proposed SmPC.

2.5.3.2.3.2 Cardiovascular function

Diurnal variation in the synthesis of endogenous melatonin plays a role in the synchronisation of molecular circadian clocks in peripheral tissues, including those of the cardiovascular system, and is associated with diurnal variations in cardiovascular functions such as heart rate, blood pressure, endothelial function and fibrinolytic activity

[REDACTED] In some cases, it is unclear to what extent such effects are due to a direct action(s) of melatonin or to an indirect action(s) such as modulation of other neurohormones that affect the cardiovascular system. The hypotensive effect of endogenous melatonin may involve a direct effect on the hypothalamus, vasodilation (smooth muscle relaxation) of the arterial wall, and possibly also melatonin's antioxidant properties ([Alternative Medicine Review 2005](#)). Individuals with hypertension have been found to have lower melatonin levels than normo-tensive subjects, and numerous cardiac conditions are a consequence of free radical damage and processes involving an inflammatory response ([REDACTED]) these effects of melatonin are addressed in [Section 2.5.3.2.3.7 Other effects](#).

A study ([REDACTED]) in which 791 adult outpatients (aged 18 – 80 yr) with primary insomnia received 2 mg melatonin (prolonged-release) or placebo 1 – 2 h before bedtime for 3 weeks found no effect of melatonin on pulse, blood pressure, or electrocardiogram measured during a daytime clinical examination, consistent with the findings of a previous study ([REDACTED]) involving ingestion of a single dose of 2 mg melatonin (prolonged-release). A crossover RCT ([REDACTED]) in which 23 children and adolescents (6 – 14 years) with ADHD and initial insomnia ingested 5 mg melatonin ('short-acting') or placebo 20 minutes before bedtime for 30 days found vital signs to be unaffected by melatonin.

A crossover RCT ([REDACTED]) in which 10 healthy subjects and 11 normotensive, normoalbuminuric type 1 diabetics (8 males, 3 females; 14 – 18 yr) ingested 5 mg IR melatonin or placebo 0.5 h before bedtime for 1 week found the normal night time decline

in systolic blood pressure (BP) to be only slightly increased (17.8 ± 4.4 vs. 16.0 ± 3.0 mmHg) in the diabetic subjects while on melatonin. A crossover RCT [REDACTED] in which 16 adult men (36 – 68 years) with mild-to-moderate, uncomplicated, untreated essential hypertension were randomised to 2.5 mg melatonin (slow-release) or placebo 1 hour before bedtime for 3 weeks found melatonin to enhance the normal night time reduction in systolic and diastolic blood pressure by 6 and 4 mmHg, respectively. A RCT [REDACTED] in which 60 patients (75% men, 48 – 80 years) with coronary artery disease and an abnormal circadian pattern of blood pressure (i.e. non-dipping night time BP) were randomised 2:1 to 5 mg melatonin ('short-acting'), or placebo, before sleep (in addition to existing medication) for 90 days reported that blood pressure patterns (determined by 24-h monitoring) normalised in 35% of patients in the melatonin group compared to 15% in the control group (not statistically significant). The authors stated that this effect occurred via a decrease in night time BP, but also by an increase in daytime BP, though the absolute differences between the interventions for the latter effect were small (2.6 and 0.3 mm Hg for systolic- and diastolic BP, respectively). The authors considered their data to indicate that melatonin has the potential to induce hypertension patients with 'high normal' blood pressure. Another cross-over RCT specifically investigated the pharmacodynamic effect of melatonin (5 mg; IR; given at 22.30 hr for 4 weeks) on 47 (27 male and 20 female) nifedipine-treated mild to moderate essential hypertensive outpatients [REDACTED]. Patients had their heart-rate and BP monitored for 24 h at the end of each treatment period, with the end results showing a significant increase in heart-rate and BP (6.5 and 4.9 mm Hg for systolic- and diastolic BP, respectively) when patients were treated with melatonin. However, beyond reports of drowsiness and weakness in 15 and 10 patients, respectively, taking melatonin, no side-effects were reported. Finally, a study investigating 4 RCT of 3 and 28 week (0.1 mg; 1 mg; 2 mg; 5 mg; slow-release) melatonin treatment of (treated) hypertensive patients (age > 55 years) did not report differences in day-time BP between melatonin-treated or untreated groups [REDACTED]. However, the study design did not allow the deduction of drug-specific effects or interactions, as several patients were treated with multiple antihypertensive drugs.

Given the above as well as other *in vitro* and animal studies, concerns have been raised for potential pharmacodynamic interactions of melatonin with anti-hypertensive drugs (reversal of their anti-hypertensive effect), especially calcium channel blockers, leading to a potentially problematic increase in BP in some patients [REDACTED]. However, none of the studies on this patient group observed any significant adverse events even after melatonin treatment for up to 1 year. Hence, whether short-term use of melatonin as intended for the Applicant's product has any effect on BP or leads to significant adverse events in this patient group remains to be investigated.

Reviews addressing the safety of melatonin (see [Section 2.5.5.5.2 Reviews addressing melatonin safety](#)) have not identified any relevant concerns in relation to intake of melatonin in a manner consistent with the posology proposed for the Applicant's product.

The proposed SmPC for the Applicant's product does not contain any warning relating to effects on blood pressure control or use by persons with hypotension or hypertension, though hypertension is listed as an uncommon undesirable effect in Section 4.8 Undesirable effects (see [Section 2.5.5.8 Conclusions on safety and proposed undesirable effects to be listed](#)). Moreover, the potential pharmacodynamic interactions with Nifedipine and other calcium-channel blockers are mentioned in [section 4.5 in the SmPC](#).

2.5.3.2.3.3 Immune system function

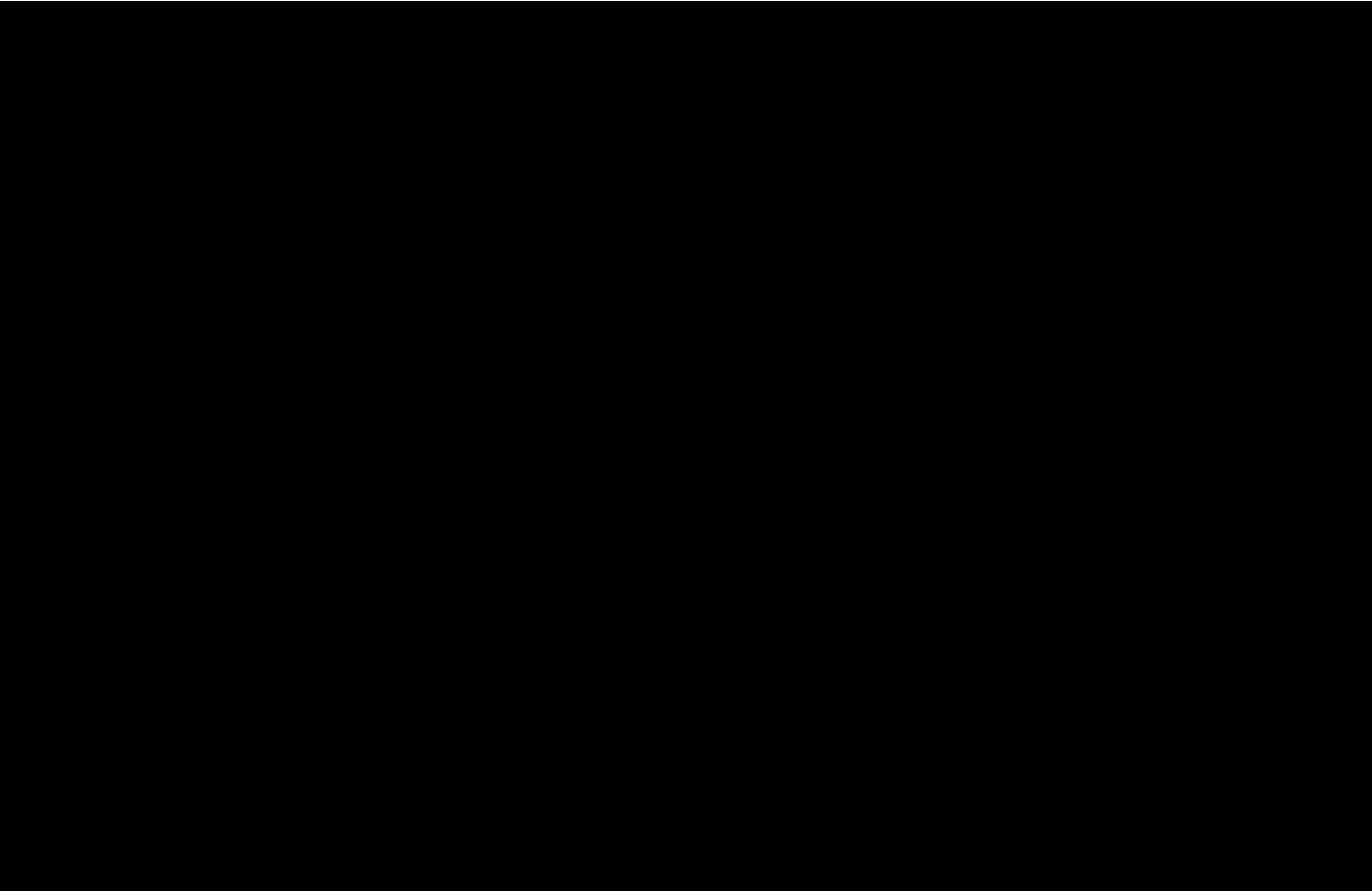
Interaction between endogenous melatonin and the immune system has been extensively documented

the following summary is based primarily on these references.

The immune system is modulated by different environmental signals including light, transduced by the diurnal pattern of melatonin secretion by the pineal gland. As melatonin is also synthesised by the retina and in other parts of the body (notably leukocytes and the intestinal mucosa) the immune system may be affected by melatonin originating in various organs. Peripheral blood mononuclear cells synthesise biologically relevant quantities of melatonin, indicating potential intracrine and paracrine roles of melatonin in immune regulation.

Mechanisms by which melatonin enhances the immune response are not clear, though it appears to increase phagocytosis and antigen presentation, and to promote T cell differentiation toward the type 1 helper T cells (Th1) phenotype. Activation of the immune system is mediated by the regulation of gene expression of cytokines in the spleen, thymus, lymph nodes and bone marrow. Natural killer cell activity and production are increased by melatonin administration. Although many studies have implicated melatonin as a positive regulator of the immune system, other reports have also suggested that melatonin could act as an anti-inflammatory agent through inhibition of immune responses. An anti-inflammatory action may be partly mediated by induction of type 2 helper T lymphocytes (Th2) producing interleukin (IL)-4 and inhibiting Th1 function. Both membrane and nuclear melatonin receptors have been identified in leukocytes; membrane receptors were found mostly on CD4+ T lymphocytes, but also on CD8+ T and B cells. Through these receptors, melatonin modulates the proliferative response of stimulated lymphocytes.

Melatonin has pleiotropic effects on various phases of inflammation. It has a pro-inflammatory role at an early phase through activation of pro-inflammatory mediators such as phospholipase A2, lipoxygenase and cytokines such as IL-1 and tumor necrosis factor alpha (TNF α). In contrast, when the inflammatory process proceeds toward the chronic phase, melatonin has a negative effect. The antagonistic role of melatonin on chronic inflammation is due to downregulation of mediators such as phospholipase A2, lipoxygenase and cytokines, induction of a survival pathway in leukocytes and blocking of oxidation by its antioxidant properties.



Safety reviews of melatonin summarised in [Section 2.5.5.5.2 Reviews addressing melatonin safety](#) have not raised relevant secondary pharmacology / safety pharmacology concerns.

In summary, literature data do not suggest that short-term ingestion of doses melatonin comparable to the recommended doses for the Applicant's product is likely to have an adverse effect on the immune system. However, data for the potential of melatonin to exacerbate or induce an autoimmune disorder are limited.

Safety issues and adverse effects relating to immune system function during melatonin treatment are addressed in [Section 2.5.5.6.1.1 Immune system adverse effects](#), which also summarises safety information relating to the immune system included in the proposed SmPC.

2.5.3.2.3.4 Reproductive functions

The *Non-clinical Overview* notes that endogenous melatonin influences reproductive functions in seasonally breeding mammals⁴⁶, with an important action being modulation of annual gonadal hypertrophy⁴⁷. In male rats, moderate exposure to exogenous melatonin increases sexual functions, whereas high doses have inhibitory effects in male⁴⁸ and

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

female rats. Daily *i.p.* injection of 100 µg melatonin for 19 days to female mice⁴⁹ reduced the rate of fertile matings, though those mice that did become pregnant carried their litters to term and delivered as many pups per litter as controls. Exposure of female rats to large s.c. doses of melatonin (starting on Day 1 of pregnancy) and ewes to s.c. melatonin before and for 5 days after mating did not affect pregnancy rates, though literature data are inadequate to permit evaluation of the effect of oral melatonin on the fertility of female animals, and essentially no fertility data is available for male animals. Administration to rats of oral dose of melatonin up to 200 mg/kg/d⁵⁰ during Days 6 to 19 of gestation⁵¹ did not affect serum 17 β-estradiol, progesterone, prolactin, or luteinising hormone (LH) levels or glandular area of mammary tissue in mothers, nor prenatal survival, fetal body weight, or incidences of fetal malformations and variations in their offspring.

Numerous studies have examined the effects of melatonin on reproductive endocrinology, though the number of studies addressing reproductive function are fewer. The following synopsis is based on a numbers of recent reviews

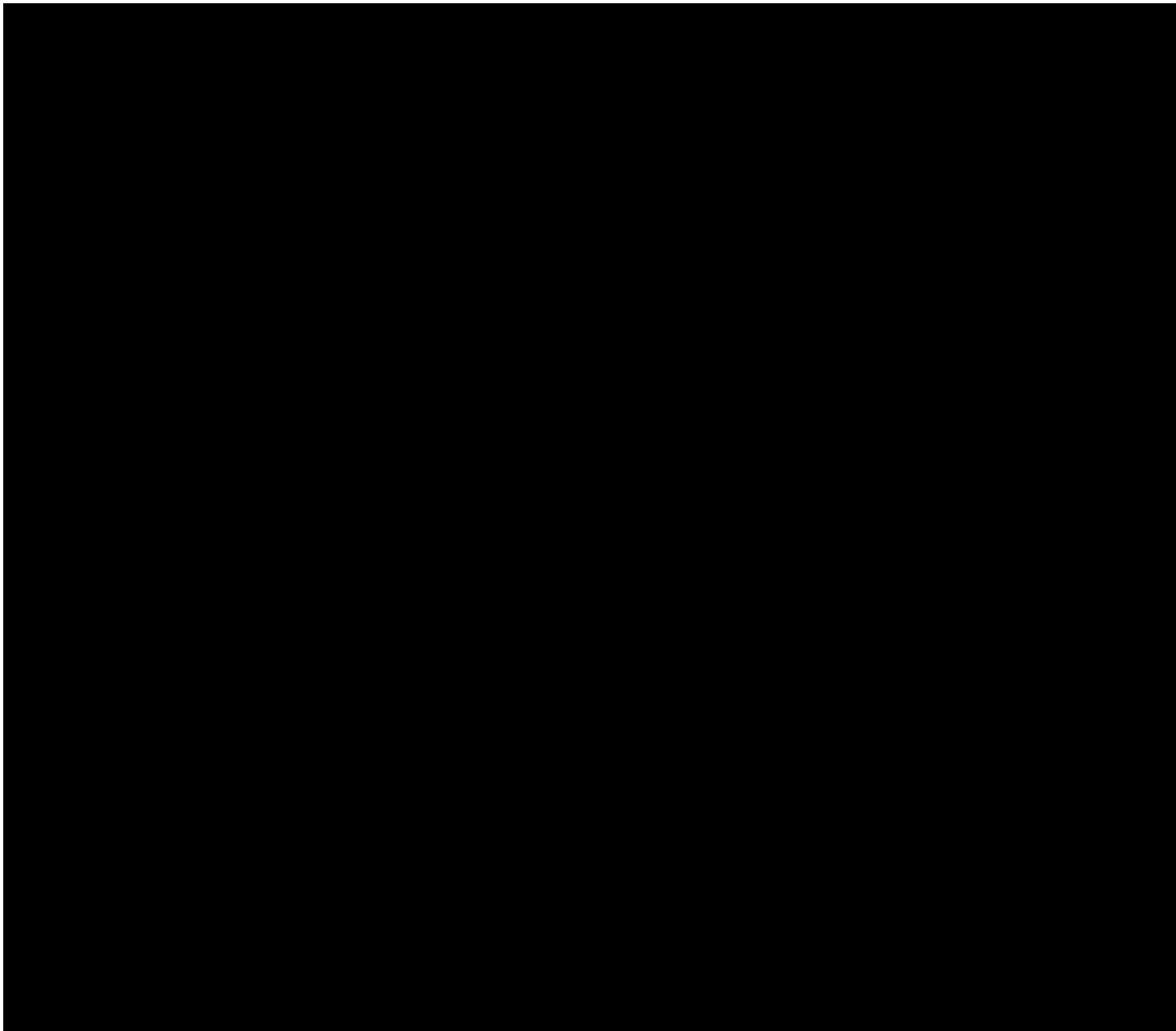
The synthesis and presence of melatonin in the human ovary and testis reflect its potential intra-, auto-, and paracrine regulation of reproductive physiology, with implications for the quality of the ovum and sperm. Melatonin concentration in pre-ovulatory follicular fluid of the human ovary is positively correlated, though significantly higher, than that in serum. Consequently, follicular fluid melatonin level (like serum level) displays circadian and circannual rhythms, which have been speculated to relate to human fertility. Human follicular cells possess melatonin receptors, and mature follicles contain higher amounts of melatonin than immature follicles. Their melatonin content is positively correlated with progesterone production, suggesting a regulatory role for melatonin on human reproduction and/or local steroidogenesis. Melatonin may be synthesised in granulosa cells and released into the follicular fluid. The capacity of melatonin to protect oocytes from molecular damage by reactive oxygen species is documented. After ovulation, luteinisation of the developing corpus luteum and the production of progesterone may also be assisted by melatonin. Melatonin modulates pituitary prolactin secretion in many seasonally breeding animal species, and might have such an effect in humans.

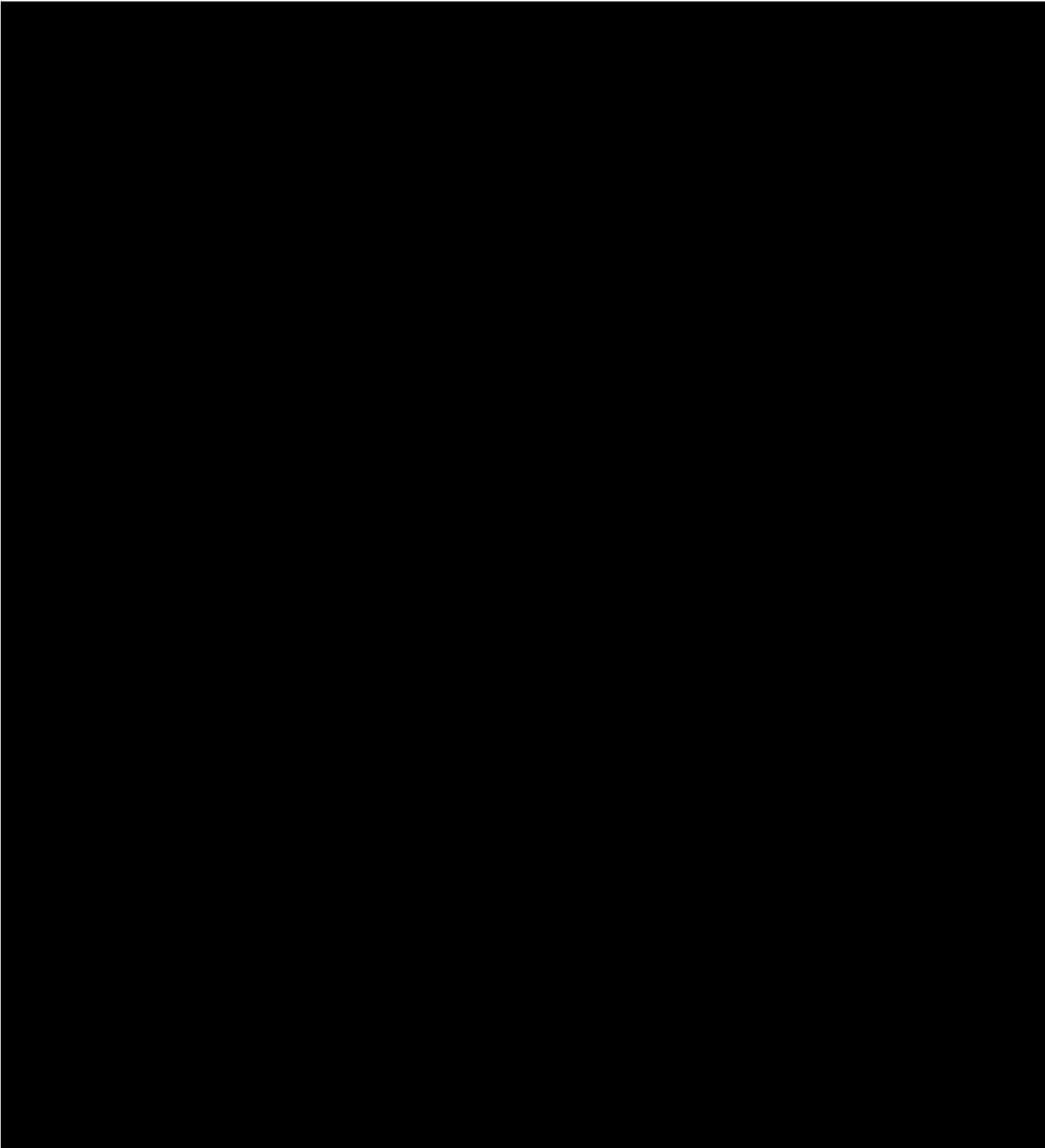
Enzymes for melatonin synthesis and melatonin binding sites are present in rat testis interstitial cells, suggesting that melatonin is produced in the testis and may exert specific actions there. *In vitro* studies suggest that melatonin or its metabolites are able to protect human sperm from oxidative damage. Human seminal fluid contains melatonin, and spermatozoa express melatonin receptors. Melatonin stimulates flagellar motility. Melatonin secreted by the pineal gland may indirectly influence male reproduction by binding to specific receptors and thereby inhibiting the production of both gonadotrophin-releasing hormone (GnRH) and LH. In the testis melatonin inhibits testosterone production and may improve sperm quality due to its antioxidant activity.

The full-term placenta synthesises melatonin and expresses MT1 and MT2 receptors. Little is known about the maturation of the placental melatonin-generating system during the earlier stages of pregnancy. Melatonin is transferred from mother to fetus, thus the fetus receives a photoperiodic signal during gestation which may be necessary for synchronising fetal physiology. Throughout gestation, maternal serum melatonin gradually

increases, reaching maximal values at the time of delivery; after parturition the values return to normal levels. In animals, chronodisruption during pregnancy can have deleterious effects on the health of progeny, including metabolic, cardiovascular, and cognitive dysfunction. It is likely that melatonin plays a role in the fetal-maternal interface, helping to maintain a successful pregnancy.

During the prepubertal period until adolescents become fertile, mean daily synthesis of melatonin is high relative to values in adults. The level drops throughout puberty then remains constant until 35 – 40 years, after which it gradually decreases. During all life-stages, melatonin displays circadian rhythmicity, with some degree of seasonal variation. Although humans are not seasonal breeders, they reportedly display some variability in conception- and birth rates throughout the year. These changes have been associated with apparent seasonal variations in melatonin level⁵². Of relevance to melatonin treatment are observations that high melatonin levels have been related to low reproductive rates and hypothalamic amenorrhea, though causality has not been established.





In summary, ingestion of large single doses of melatonin and of daily doses comparable to the standard recommended dose (3 mg) for the Applicant's product for a minimum of 4 weeks are not associated with adverse changes to female endocrine function, particularly reproductive endocrinology. This also appears to be the case with longer-term use of the melatonin-receptor agonist, ramelteon. When effects of melatonin have been seen, they tend to be consistent with the capacity for endogenous melatonin to decrease gonadotrophin (LH, FSH) production, with a very large oral dose having an anovulatory effect. Typical therapeutic doses (3 – 6 mg) of melatonin have been found to ameliorate oxidative stress in luteinised granulosa cells. Based on the above, it is considered unlikely

that recommended use of the Applicant's product (maximum of 6 mg for a maximum of 5 days) will have significant adverse effects on female reproductive endocrinology. The implications of the above findings for use of the Applicant's product by pregnant women or women planning a pregnancy are addressed in [Section 2.5.5.9.6 Pregnancy and lactation](#) (Safety in special groups and situations).

Endocrine function in men

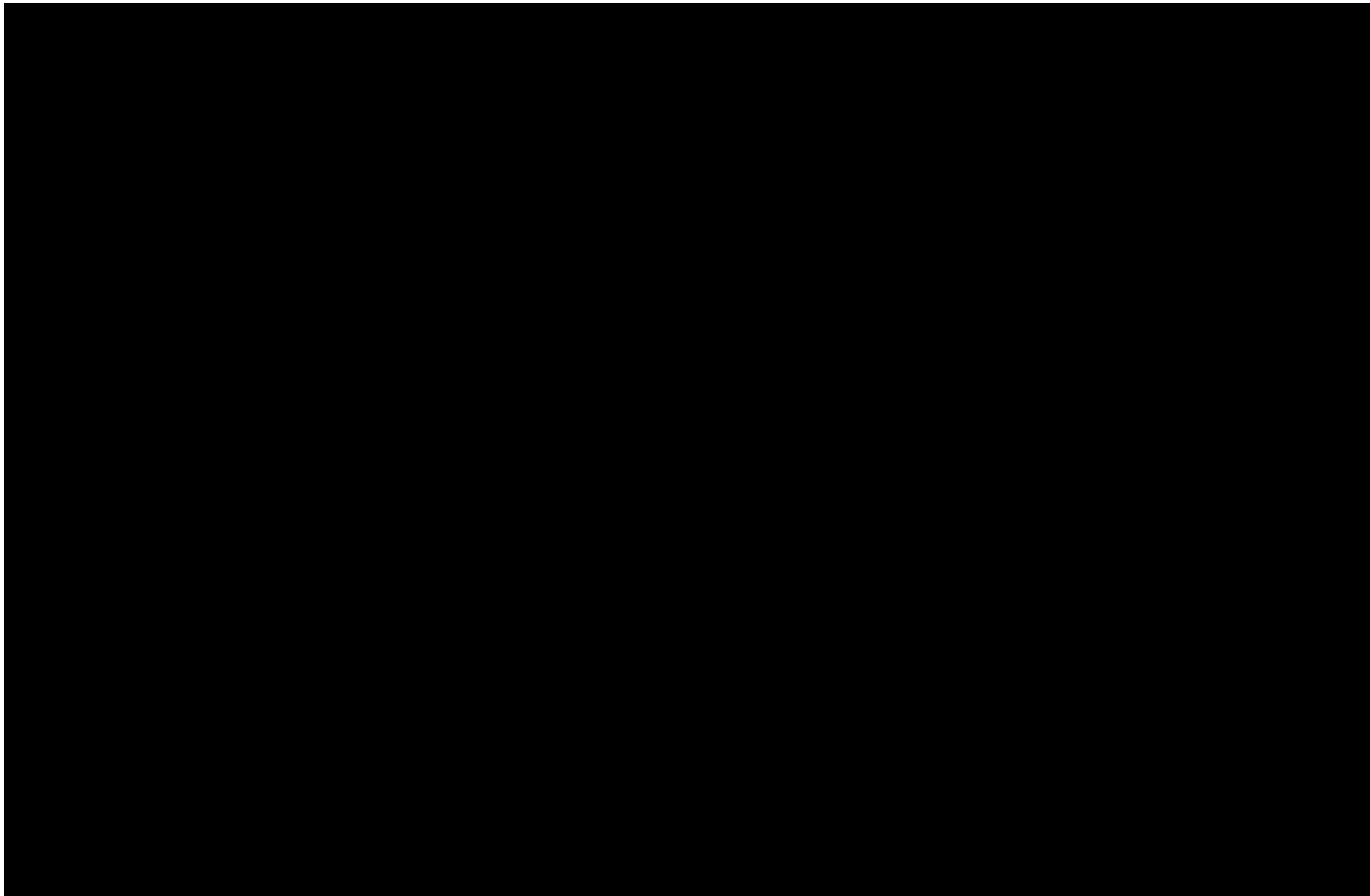
In summary, ingestion of a large single dose of melatonin and of daily doses comparable to the upper recommended dose (6 mg) for the Applicant's product for a minimum of 4

weeks is not associated with adverse changes to male endocrine function, particularly reproductive endocrinology. This also appears to be the case with longer-term use of the melatonin-receptor agonist, ramelteon. Based on the above, it is considered unlikely that recommended use of the Applicant's product (maximum of 6 mg for a maximum of 5 days) will have significant adverse effects on male reproductive endocrinology. The implications of the above findings for use of the Applicant's product by men planning a pregnancy are addressed in [Section 2.5.5.9.6 Pregnancy and lactation](#) (Safety in special groups and situations).

Overall summary on endocrine function and reproductive endocrinology

As melatonin is arguably the body's primary phase-setting hormone, changes in the timing of melatonin secretion can be expected to affect the diurnal rhythm of other hormones, including reproductive hormones. In this regard, there is good evidence that administration of exogenous melatonin during the day⁵³ can alter the *timing* of the diurnal secretory patterns of other hormones. Typical therapeutic doses of melatonin have, at most, a slight, transient effects on the *levels* of other hormones; an effect on prolactin cannot be discounted.

Fertility, pregnancy and lactation

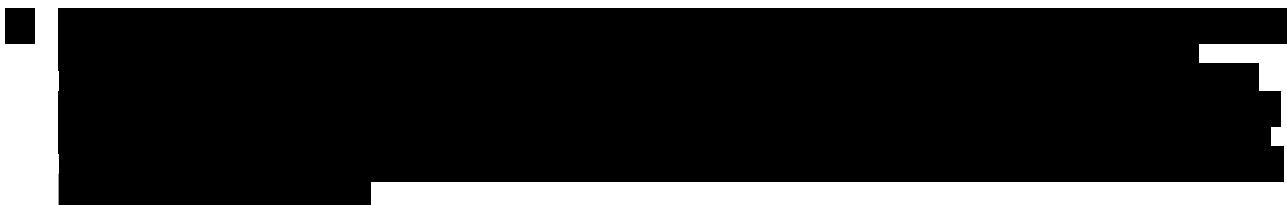


In summary, information on the effects of exogenous melatonin on human ova, sperm, and fertility are limited. Doses comparable to those recommended for the Applicant's product have beneficial effects when taken by women undergoing IVF treatment. Very large oral doses of melatonin have an anovulatory effect, though the doses required are not considered relevant to use of the Applicant's product. Data for effects on sperm are contradictory, though there is no data indicating adverse effects associated with short-term (days-to-weeks) intake of doses comparable to those (3 or 6 mg) recommended for the Applicant's product. In the *Conclusions* section (page 783) of their review of the role of melatonin in human reproduction, [REDACTED] note that "*Currently, the balance of evidence from clinical studies suggests that the effect of melatonin on human reproductive processes such as ovulation and fertility is attenuated* [compared to that in animals]."

Safety issues and adverse effects relating to melatonin treatment and fertility are addressed in [Section 2.5.5.9.6 Pregnancy and lactation](#), which also summarises safety information relating to fertility in the proposed SmPC.

Pregnancy

[REDACTED] noted that endogenous melatonin levels are higher during pregnancy (see Figure 4a of [REDACTED] for confirmation), and [as melatonin readily crosses the placenta] maternal melatonin rhythm serves as a signal to the fetus to entrain light-dark rhythms. It was also noted that maternal melatonin levels may influence



REM sleep in the fetus. [REDACTED] confirmed that exogenous melatonin rapidly crosses the human placenta and enters the fetal circulation (see [Section 2.5.3.1.2.4 Transplacental distribution](#)) a finding considered consistent with previous studies in sheep and rhesus monkeys. However, no information on the effect of *in utero* exposure to melatonin on pre- and post-natal development in humans was identified in the literature.

Safety issues and adverse effects relating to melatonin treatment during pregnancy are addressed in [Section 2.5.5.9.6 Pregnancy and lactation](#), which also summarises safety information relating to pregnancy in the proposed SmPC.

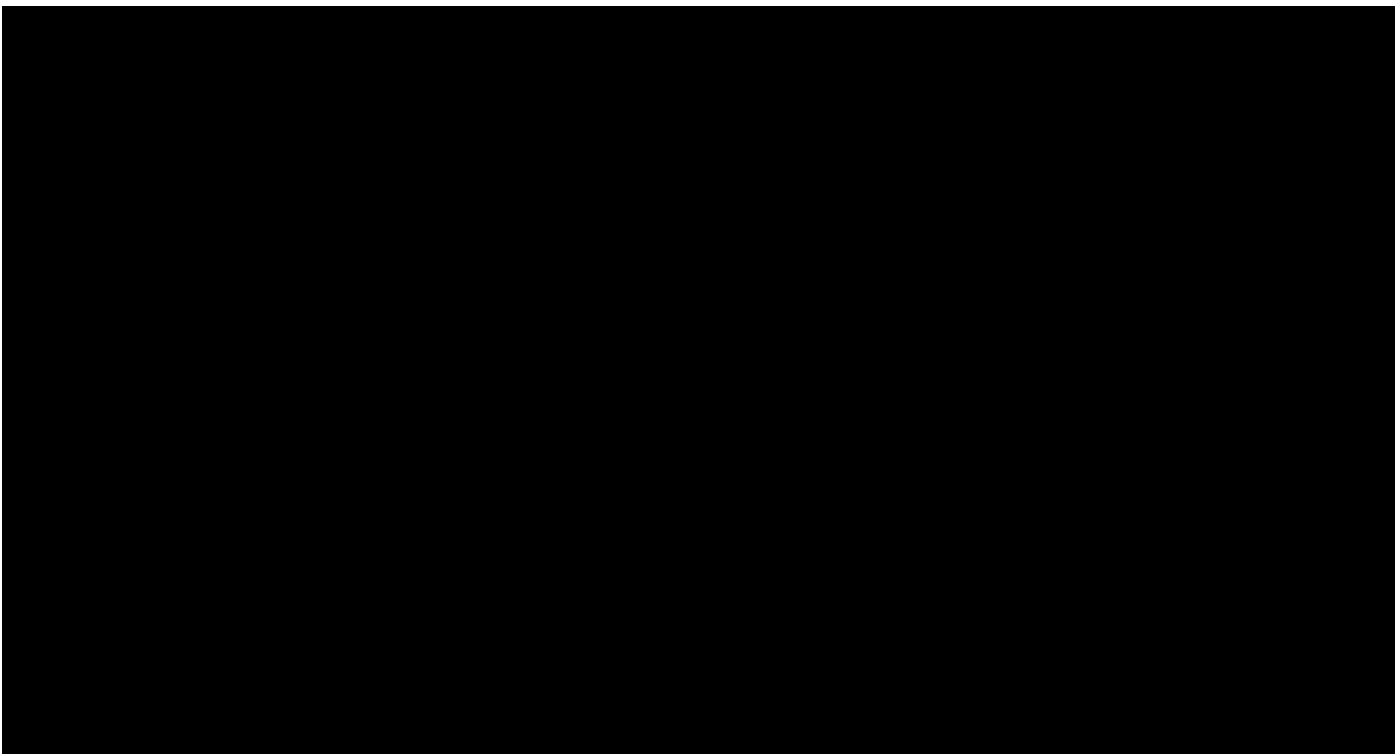
Lactation

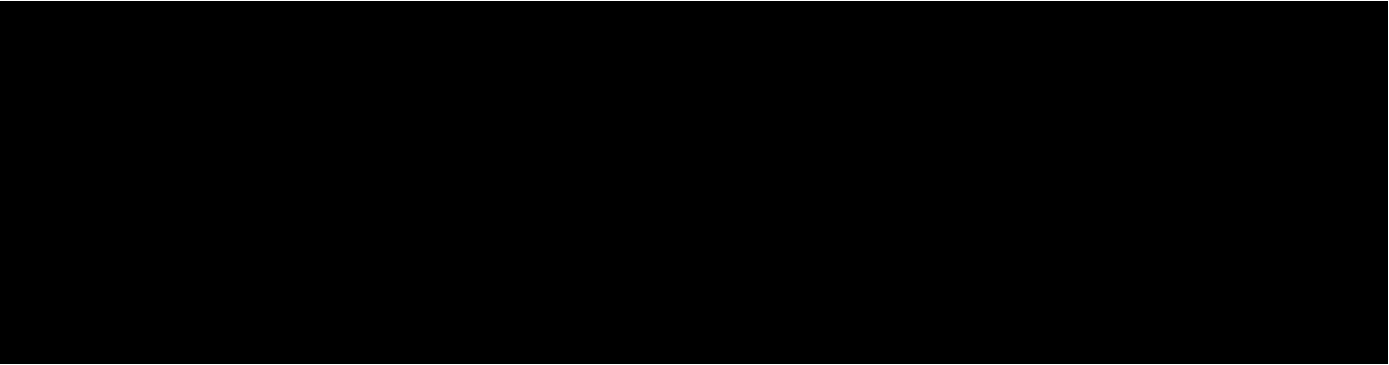
[REDACTED] reported that melatonin is secreted in human milk; the level was undetectable during the day and peaked mid-to-late night at roughly 35% of the peak (night-time) maternal serum concentration. Data for the excretion of exogenous melatonin, and its metabolites, in human milk are not available, though the data of [REDACTED] suggest that exogenous melatonin is likely to be excreted to some extent in human milk.

Safety issues and adverse effects relating to breast feeding during melatonin treatment are addressed in [Section 2.5.5.9.6 Pregnancy and lactation](#), which also summarises safety information relating to lactation in the proposed SmPC.

2.5.3.2.3.5 Sexual development

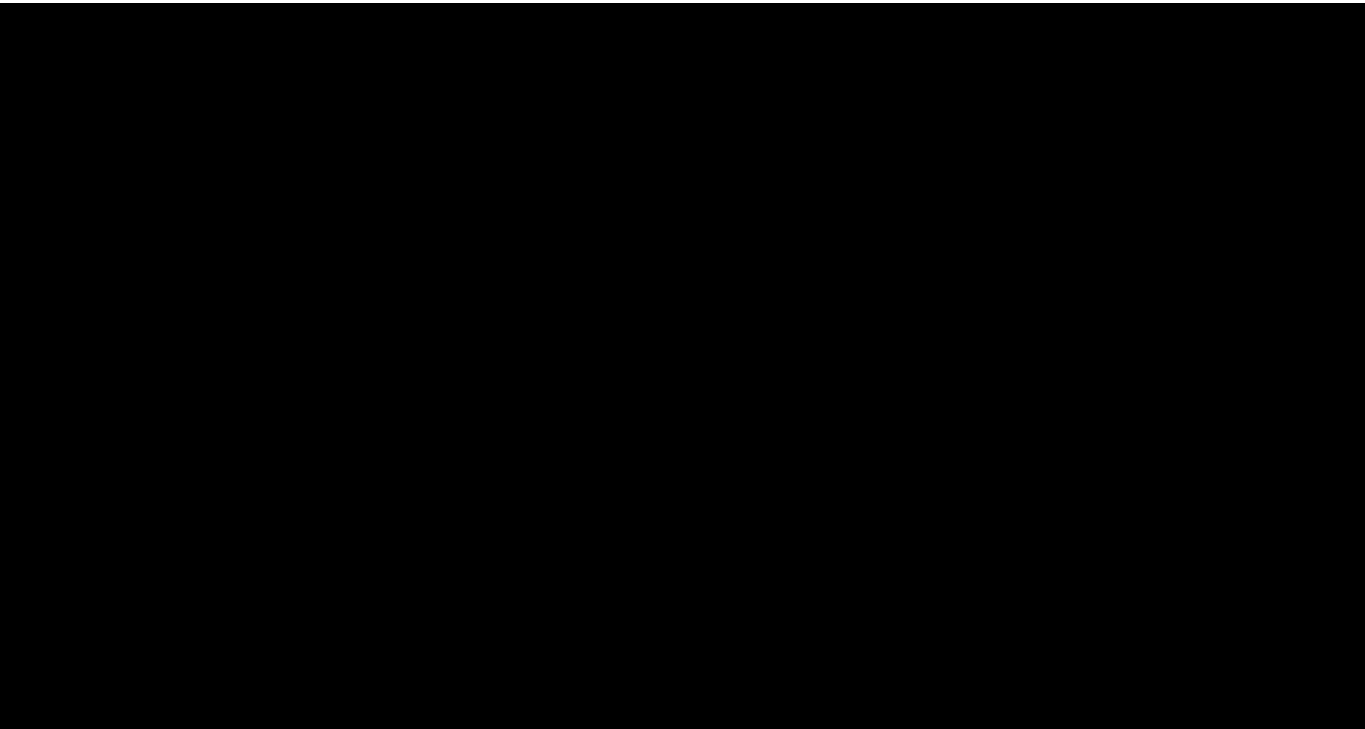
The *Non-clinical Overview* ([Section 2.4.4.5 Reproductive and developmental toxicity](#)) noted that s.c. administration of melatonin to pregnant rats has no effect on the general development of their male and female offspring but delays their sexual maturation. Subcutaneous administration of melatonin to female palm squirrels during pregnancy and post-partum reduced reproductive organ weights and delayed sexual maturation of male and female offspring. These data suggest that exogenous melatonin may influence the ontogeny and activation of the hypothalamic-pituitary-gonadal axis. However as the wild rat and palm squirrel are seasonal breeders the implications of these findings for humans are uncertain.





In summary, it is not known to what extent exogenous melatonin modulates the hypothalamic-pituitary-gonadal axis pre-puberty in humans. Limited clinical studies have not confirmed any safety concerns, however specifically designed studies have not been performed. Safety issues and adverse effects relating to reproductive function during melatonin treatment are addressed in [Section 2.5.5.6.1.2 Sexual development adverse effects](#), which also summarises safety information relating to pregnancy included in the proposed SmPC.

2.5.3.2.3.6 Analgesic effect



Safety reviews of melatonin summarised in [Section 2.5.5.5.2 Reviews addressing melatonin safety](#) have not raised relevant secondary pharmacology / safety pharmacology concerns.

In summary, the above data suggest that oral doses of melatonin comparable to the recommended dose for the Applicant's product have an analgesic action, though analgesic, sedative, and eventual anxiolytic effects may, in fact, contribute to the efficacy of melatonin taken at bedtime for treatment of jet-lag. Considering the posology and brief

- 57 Potent, dose-dependent analgesic effects in experimental studies; analgesic benefits in patients with chronic pain (fibromyalgia, irritable bowel syndrome, migraine).
- 58 Morphine and fentanyl use was significantly reduced in 2 of 2 studies, and diclofenac (NSAID) use significantly reduced in 1 of 1 study.

duration of a treatment period proposed for the Applicant's product, the apparent analgesic effect of melatonin is not considered a safety pharmacology concern.

2.5.3.2.3.7 Other effects

Melatonin is a potent free radical scavenger. It directly scavenges the highly reactive hydroxyl radical, increases the level of several antioxidative enzymes (notably superoxide dismutase and glutathione reductase), and inhibits the pro-oxidative enzyme, nitric oxide synthase. Melatonin has such effects at both physiological and pharmacological concentrations ([REDACTED]

[REDACTED]. Melatonin also has anti-inflammatory effects via down-regulation of pro-inflammatory cytokines, inhibition of nitric oxide and methylene-dioxvamphetamine (MDA) production, and modulation of prostaglandin profile ([REDACTED]

Oral melatonin has been found to alter alpha-theta activity in the EEG in a manner consistent induction of sleep [REDACTED]. In 2 consecutive [REDACTED] in which a total of 14 outpatients (9 men and 5 women; mean age ~ 51 years) with diverse neuropsychiatric sleep disorders and reduced REM sleep duration ingested 3 mg IR melatonin or placebo between 22:00 – 23:00 hr daily for 4 weeks, no adverse effect on EEG (measured at baseline and on the last 2 nights of treatment) was observed. Melatonin significantly increased the percentage of REM sleep and REM continuity compared to placebo. Melatonin and placebo were not distinguishable by frequency, intensity, quality or content of dreams.

2.5.3.2.4 Conclusions on pharmacodynamics

Melatonin is a hormone, produced primarily by the pineal gland, that has an important role in regulating circadian rhythms. The circadian pacemaker ('body clock') in the SCN of the hypothalamus modulates melatonin synthesis and secretion from the pineal gland. Once melatonin appears in the plasma it enters the brain and binds to melatonin receptors (MT1 and MT2) in the hypothalamus (and other areas of the brain), forming a feedback loop. The high density of melatonin receptors in the SCN suggests that melatonin affects the sleep-wake cycle by acting on these receptors. The presence of melatonin receptors in multiple sites in the body, and the capacity of many tissues to synthesise melatonin (that does not appear to enter the systemic circulation) indicates important roles of melatonin.

The circadian production of melatonin underlies its chronobiotic influence on biochemical and physiological processes including the endocrine and non-endocrine rhythms. The most significant regulatory factor in the production of pineal melatonin is the daily alternation of light and darkness; (day)light registered and signalled by the retina suppresses melatonin synthesis. In humans, the circadian rhythm of pineal melatonin release is highly synchronised with the habitual hours of sleep, and the daily onset of melatonin secretion correlates with the subsequent onset of nocturnal sleepiness.

Regarding primary pharmacodynamics, exogenous melatonin can be expected to limit and treat symptoms of jet-lag by a) hastening the re-entrainment of circadian rhythmicity, including the rhythmicity of endogenous melatonin secretion, and b) via a direct sleep-inducing / maintenance action.

Oral melatonin at typical pharmacological doses shifts circadian rhythms in humans according to a phase-response curve that is nearly opposite the phase-response curve for light exposure. Melatonin delays circadian rhythmicity when administered after dim light

melatonin onset (DLMO) and advances it when administered before DLMO. The former occurs when melatonin is taken following a westward flight, while the latter occurs following an eastward flight. Likewise, administration of melatonin during the day advances the phase of the diurnal plasma cortisol profile.

Peak in melatonin production coincides with the nocturnal trough in CBT, and the evening fall in CBT is strongly correlated with the rise in plasma melatonin level following DLMO. Oral melatonin reduces sleep onset latency, with some evidence that it improves sleep quality and sleep architecture (percentage REM sleep). The sleep-inducing effect is evident regardless of the time of administration, though – not unexpectedly – there is a degree of attenuation with administration around DLMO. The effects of oral melatonin on sleep may be mediated by a reduction in CBT, and possibly also by potentiation of the effects of gamma-aminobutyric acid (GABA) via direct interaction with GABA receptors.

Regarding secondary PD and safety pharmacology, typical therapeutic doses of melatonin do not appear to adversely affect the 'core safety battery' (i.e. nervous-, respiratory, and cardiovascular systems). Limited data suggests that ingestion of melatonin in close proximity to a meal (especially if carbohydrate-rich) may transiently impair glycaemic control, though longer-term (minimum 3 weeks) ingestion (typically at bedtime) of melatonin does not appear to adversely affect fasting blood- glucose or lipids in healthy persons, nor fasting blood- glucose, HbA1c or lipids in Type 2 diabetics. Exogenous melatonin does not appear to have an adverse effect on the immune system in general, though limited data suggest that it may potentially exacerbate or induce autoimmune disorders. Typical therapeutic doses of melatonin may have mild analgesic and anxiolytic effects, though neither is considered a concern in relation to use of the Applicant's product. Melatonin is a potent free radical scavenger, and has anti-inflammatory effects via down-regulation of pro-inflammatory cytokines, inhibition of nitric oxide and methylene-dioxyamphetamine (MDA) production, and modulation of prostaglandin profile.

As melatonin is the body's primary phase-setting hormone, changes in the timing of melatonin secretion can be expected to affect the diurnal rhythm of other hormones, including reproductive hormones. There is good evidence that administration of melatonin during the day can alter the *timing* of the diurnal secretory patterns of other hormones. However, typical therapeutic doses of melatonin have, at most, only a slight, transient effect on the *level* of other hormones. Ingestion typical therapeutic doses of melatonin for 4 weeks is not associated with adverse changes to female or male endocrine function, particularly reproductive endocrinology. This also appears to be the case with longer-term use of the melatonin-receptor agonist, ramelteon.

The synthesis and presence of melatonin at multiple sites in the ovary and testes reflect its potential role in intra-, auto-, and paracrine regulation of reproductive physiology, though effects of melatonin on reproductive processes (such as ovulation and fertility) in humans appears attenuated compared to animals. No clear adverse effects on female or male fertility, or on pregnancy, have been observed with typical therapeutic doses of melatonin, though data are limited. When effects have been seen (at very high doses), they tend to be consistent with the capacity of endogenous melatonin to decrease gonadotrophin (LH, FSH) production. Exogenous melatonin has been found to ameliorate oxidative stress in luteinised granulosa cells, and to have beneficial effects when taken by women undergoing IVF treatment.

Administration of melatonin to pregnant rats and palm squirrels has been found to delay sexual maturation of their male and female offspring, and to reduce reproductive organ weights in the latter species. These data suggest that exogenous melatonin may influence the ontogeny and activation of the hypothalamic-pituitary-gonadal (HPG) axis. These

species are seasonal breeders, in which the annual rhythmicity of melatonin secretion modulates gonad hypertrophy and reproductive activity in general. It is not known to what extent exogenous melatonin modulates the HPG axis pre-puberty in humans, which are not seasonal breeders. Limited clinical studies in children have not confirmed any safety concerns, however, specifically designed studies have not been performed.

2.5.4 OVERVIEW OF EFFICACY

Efficacy of melatonin for treatment of jet-lag

The intensity and duration of jet-lag are influenced by a number of parameters, of which the following are considered primary:

- number of time zones crossed (worse the more zones crossed)
- direction of travel (worse with eastward travel)
- ability to sleep while travelling
- availability and intensity of local circadian time cues
- individual differences in phase tolerance (tendency to be worse in older people)

[REDACTED]

[REDACTED]

Participants

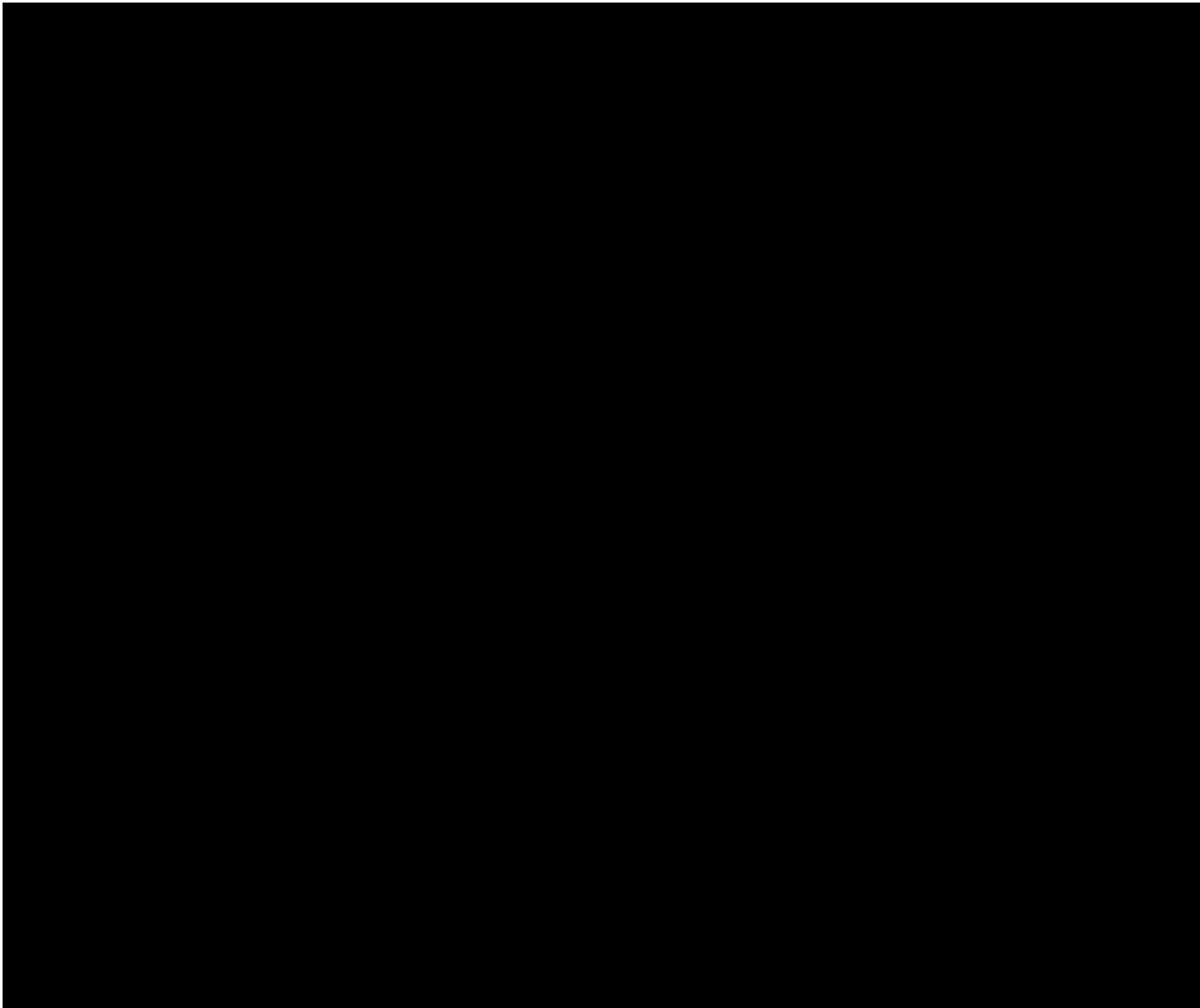
[REDACTED]

10 jet-lag studies travelled in groups. The overall study population is also considered representative of intercontinental flight passengers in that participant age ranged from the mid 20s to mid 60s in most studies (though no study enrolled persons under 18 or over 68 years⁶⁴), 64% were men, and reasons for travel included work and leisure, though physicians and university staff are over-represented.

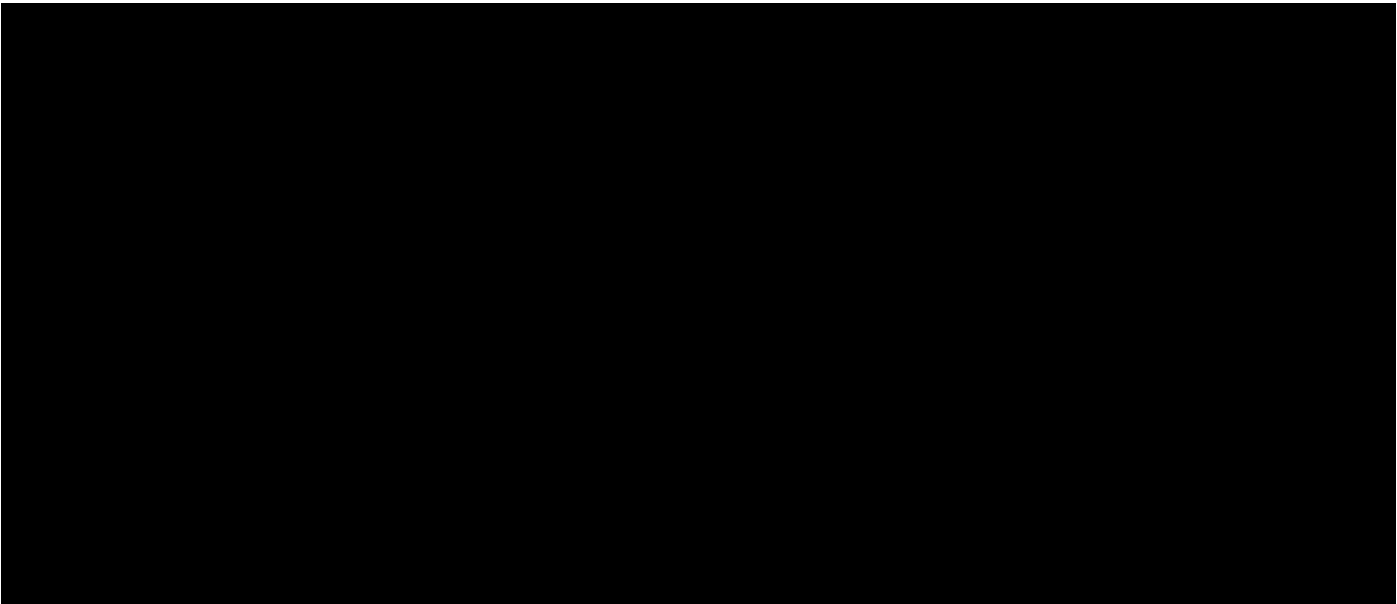
Interventions: nature, dose, timing, and duration of intake

[REDACTED]

[REDACTED]



Efficacy parameters



[REDACTED]

[REDACTED] Efficacy findings and their implications

Efficacy

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED] to this study are addressed
under the heading *Study size bias* in [Section 2.5.4.1.3 Potential sources of error](#).

[REDACTED]

In summary, global efficacy generally made an important contribution to the assessment of the efficacy of melatonin in the 10 jet-lag studies and, across the studies, indicated that melatonin reduced the degree of overall symptoms by ~ 44% and their duration by ~ 32%. The reduction of global jet-lag appears primarily based on improvements in night-time sleep (reduced sleep onset latency, improved sleep quality) and combined improvements in daytime- tiredness, mood, and energy / fatigue. Effects on physical and mental performance are unclear.

Overall, [REDACTED] t short-term (~ 4 – 5 days) intake of melatonin at bedtime at destination results in a clinically significant reduction in the severity and duration of symptoms of jet-lag. This opinion is consistent with those of several reviews of the pathophysiology of jet-lag and its treatment with melatonin. At the beginning of their *Conclusions* section (page 76) [REDACTED] write: “*Melatonin is an established agent that is useful in providing both a synchronizing action and a soporific effect in jet lag. Its utility has been especially well documented for eastward flight of 5 – 9 h as are the appropriate timing and dosage of administration. It may also be useful for shorter periods of eastbound travel for those prone to jet lag symptoms. ... For westward flight many fewer studies have been done, perhaps because the majority of people have innate circadian rhythms longer than 24 h and can thus acclimatize more rapidly to westbound travel. Nonetheless melatonin treatment may be beneficial.*” Under the heading *Treatment of jet lag: Timed melatonin administration* (page 108) [REDACTED] writes: “*Melatonin administration is the most studied treatment for jet lag and the evidence is quite compelling that it can accelerate adaptation to a new time zone.*” Under the heading *Melatonin in jet lag* (page 21) [REDACTED] writes: “*With few exceptions, melatonin’s usefulness for ameliorating the symptoms of jet lag has been compellingly demonstrated in numerous investigations.*”

The capacity for melatonin treatment to shorten the duration of jet-lag, and thus also to reduce its severity on a given day post-flight, is supported by data for the effect of melatonin at bedtime at destination on resynchronisation of the rhythms of endogenous melatonin and cortisol. [REDACTED] found resynchronisation of melatonin rhythm and cortisol rhythm⁷⁰ to be more rapid in subjects receiving melatonin. [REDACTED] found that melatonin treatment did not have clear effect on resynchronisation of melatonin rhythm but that resynchronisation of cortisol rhythm was more rapid⁷¹. [REDACTED] found intake of 3 mg melatonin at bedtime (23:00 hr) on Days 2 – 4 after a 8-h eastward flight to result in more rapid resynchronisation of endogenous melatonin rhythm than when the same subjects had not taken melatonin on a previous, comparable flight (daily shift in re-entrainment 76 minutes with melatonin vs. 31 minutes without). [REDACTED] found that ingestion of 5 mg melatonin daily before, during, and after a 7-h eastward flight to hasten resynchronization of cortisol rhythm during the 4 days post-flight.

[REDACTED]

[REDACTED]

[REDACTED]

Dose recommendations

[REDACTED]

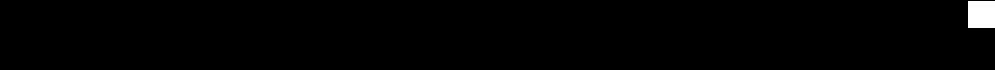
[REDACTED]). However, inter-individual variability in severity of jet-lag symptoms in the general population is large ([REDACTED]), as is inter-individual variability in melatonin pharmacokinetics (addressed in [Section 2.5.3.1 Pharmacokinetics](#)).

[REDACTED] a standard dose of 3 mg daily (for a maximum of 5 days), and that a 6 mg dose may be taken if the standard dose does not adequately alleviate symptoms. It also proposes that the dose that adequately alleviates symptoms should be taken for the shortest period. This dose range is comparable to that for a 3 mg melatonin tablet authorised in Hungary with an indication that includes alleviation of sleep disturbances due to jet-lag⁷⁵.

Timing of initiation of treatment

S.

Melatonin was taken at bedtime in each of the 10 jet-lag studies included in the Cochrane Review of melatonin for jet-lag (Cochrane, updated 2008); 'bedtime' was defined (as between 22 and 23/24 hr) in 5 of the 10 studies.



[REDACTED]

Based on the [REDACTED] information, [REDACTED] that melatonin should be taken at habitual bedtime.

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

Based on the [REDACTED] information, and on the efficacy of melatonin in jet-lag studies involving flights crossing ~ 8 – 9 or more time zones, the Applicant considers that its product can be taken for flights crossing a large number of time zones as long as it is taken at bedtime at destination. However, due to the potential for incorrectly timed intake of melatonin to have no effect, or an adverse effect, on re-synchronisation the product should not be taken before 20:00 hr or after 04:00 hr at destination⁸³.

Schemes in which melatonin – depending on the direction of air travel and number of time zones crossed – is taken progressively earlier or later in the evening on successive days of a treatment period have been proposed. While valid in theory, they have practical difficulties, such as the need for a range of intake times depending on the direction of travel and number of time zone crossed, and require good understanding of time-zone passage and full compliance on the part of the user in order to ensure efficacy and safety. This makes them unsuitable for use by the general population. Published clinical data is inadequate to support such schemes.

Duration of treatment

[REDACTED]

Based on the [REDACTED] information, [REDACTED] that its product should be taken for a maximum of 5 days, and that the dose that adequately alleviates symptoms should be taken for the shortest period.

Eastward vs. westward travel

[REDACTED]

Overall, the data are not considered to indicate that melatonin is less effective for treatment of jet-lag following westward travel. It can be expected that less-severe jet-lag following travel in a westward direction will result in intake of the standard (lower) dose for a shorter duration. In this regard, the Applicant proposes that the dose that adequately alleviates symptoms should be taken for the shortest period.

Potential sources of error

The Cochrane Review of melatonin for jet-lag [REDACTED], updated 2008) addresses the issue of bias. It notes that most of the trials are described too briefly and that some of the procedures used are unclear, however the design and performance of the 10 trials seem to have satisfactorily minimised selection bias, performance bias, attrition bias, and detection bias. Nine of the studies were described as double-blind; risk of bias due to blinding (allocation concealment) was considered low in 5 studies and unclear in 5 studies.

Study size bias

[REDACTED]

[REDACTED]

[Redacted]

[Redacted]

Based on the above, the Applicant does not consider there to be evidence that study size biased efficacy findings.

[Redacted]

- [Redacted]
- [Redacted]
- [Redacted]

[REDACTED]

[REDACTED]

Conclusion on melatonin for jet-lag

The data summarised above are considered to demonstrate that 3 mg IR melatonin taken at bedtime on arrival at destination for up to 5 days is effective for the treatment of jet-lag; a 6 mg dose may be required if the standard dose does not adequately alleviate symptoms. Clinical studies have found subjective ratings of overall jet-lag to be reduced by ~ 42%, and the duration of jet-lag to be reduced by ~ 33%, though data for the latter parameter are fewer. This information is generally consistent with the recommendations of a number of melatonin experts and a recent guideline ([Expert and Guideline posology recommendations for melatonin for jet-lag](#)). Mechanisms underlying the global improvement in jet-lag include hastening of the rate of re-synchronisation of endogenous melatonin rhythm and cortisol rhythm, improved sleep quality, and reduced sleep onset latency and daytime tiredness.

[REDACTED]

Expert and Guideline posology recommendations for melatonin for jet-lag.

Source	Flying eastward	Flying westward
	Melatonin may be taken on departure day at approximately 18:00 hr to initiate a phase advance, and then at bedtime in the new time zone, to reinforce phase advances and the soporific effects.	Melatonin may be taken at bedtime in the new time zone initially to phase delay, but primarily using soporific effects.
	Melatonin is effective when taken at bedtime after darkness has fallen on the first day of travel; and again in the same way on the second (and any subsequent day) of travel, and at the destination on the following few days at the same time. For many people 5 mg may be a higher dose than necessary: 2 or 3 mg may therefore be preferable to start with.	As for eastward
	To promote shifting of the body clock to an earlier time, take 0.5-3 mg at local bedtime nightly until you have become adapted to local time.	To promote shifting of the body clock to a later time, take 0.5 mg (a short-acting dose) during the second half of the night until you have become adapted to local time.
	When trying to reset the body clock to an earlier time melatonin should be taken at local bedtime nightly until becoming adapted to local time; melatonin should be taken 30 minuts before planned sleep time.	When trying to reset the body clock to a later time melatonin should be taken in the morning; melatonin should be taken 30 minutes before planned sleep time.

Efficacy of melatonin in other disorders and diseases

Due to the capacity of exogenous melatonin to modulate (re-entrain) the diurnal rhythm of melatonin synthesis and the body's circadian rhythmicity in general, and to induce and maintain sleep in particular, melatonin has been extensively studied as a treatment for circadian rhythm sleep disorders (CRSDs), both primary and secondary⁹⁴. As sleep disorders are quite prevalent in children, particularly those with neurological disabilities a sizable proportion of these studies involved children and adolescents. Melatonin has also been studied in a number of other, disparate situations including as an analgesic to treat migraine and as an adjuvant treatment (to myo-inositol plus folic acid) in women undergoing IVF o name just a few. Such situations are considered beyond the scope of this Application with regards to efficacy evaluation, though safety data from a number of such

studies are considered in [Section 2.5.5 Overview of safety](#). The following sections summarise efficacy data from a representative selection of studies and reviews of oral melatonin for treatment of circadian rhythm disorders that are considered most relevant to this Application.

Delayed sleep phase disorder (DSPD)

DSPD is arguably the most common CRSD. Affected persons have an abnormally delayed sleep-wake rhythm, characterised by difficulty initiating sleep at an appropriate time, trouble waking at a desired time in the morning, and daytime sleepiness due to inadequate night-time sleep.

Based on a review by the American Academy of Sleep Medicine (AASM) that included 3 crossover RCT and 1 study without a comparator, the AASM Task force considered there to be moderate degree of clinical certainty for the efficacy of melatonin for treatment of DSPD.

A more recent meta-analysis of RCTs of melatonin for DSPD evaluated 5 trials in adults and 4 trials in children concluded that melatonin is effective in advancing sleep-wake rhythm and endogenous melatonin rhythm in DSPD. A subsequent crossover RCT in which 20 patients with DSPD ingested 5 mg melatonin or placebo for 4 weeks with a 1-week washout period found melatonin to significantly reduced sleep onset latency (SOL) and significantly increased total sleep time (TST) in DSPD patients without (n = 12) or with (n = 8) depressive symptoms, with no adverse effects on sleep architecture. Melatonin significantly reduced depression scores in the depressed patients.

Primary Sleep disorders

A meta-analysis that included 17 RCT of varying patient populations⁹⁵ and designs that involved 284 subjects found that melatonin reduced SOL and increased sleep efficiency and total sleep time, though the size of the effects were small.

A meta-analysis of 14 RCTs in which 279 subjects with primary sleep disorders (principally insomnia and DSPD), were given melatonin (1 – 3 mg in 6 studies, 4 – 5 mg in 7 studies) or placebo for up to 4 weeks found melatonin to significantly reduce SOL, with the effect greater in DSPD than in insomnia. The effect size was considered clinically important. Sleep efficiency (measured in 10 trials) was borderline significantly greater with melatonin, while TST (measured in 13 trials), and wakefulness after sleep onset (measured in 6 trials) tended to favour melatonin.

A Scientific Opinion by the European Food Safety Authority considered a cause-and-effect relationship to be established between the consumption of melatonin and reduction of SOL. It was stated that in order to obtain the effect, 1 mg of melatonin should be consumed close to bedtime by the target population (the general population).

A meta-analysis of the efficacy of melatonin in patients with primary sleep disorders that included 19 RCTs involving 1683 subjects found that melatonin reduced SOL (by 7.1 minutes) and increased TST (by 8.3 minutes). Trials with longer duration and using higher doses resulted in greater improvements in SOL and TST.

95 Seven of the studies involved healthy persons, and 8 involved patients with insomnia.

Overall sleep quality was significantly improved in subjects taking melatonin compared to placebo.

2.5.4.2.3 Secondary Sleep disorders

[REDACTED]

[REDACTED]

Numerous studies have examined the efficacy of melatonin for shift-work, which results in sleep-wake disturbances manifest as sleepiness during the wake (night-time) period and reduced sleep duration and quality during the period (daytime) in which sleep (at least the majority) must be obtained; its serious form is referred to as shift-work sleep disorder (SWSD). A Cochrane review and meta-analysis ([REDACTED]) of pharmacological treatments for sleepiness and sleep disturbances caused by shift-work concluded that there is low quality evidence that melatonin improves sleep length by 24 minutes after a night shift, but does not improve other sleep quality parameters.

[REDACTED] Conclusions on efficacy of melatonin for other CRSDs

Current understanding of circadian rhythmicity, sleep physiology, and the pharmacodynamics of exogenous melatonin provides a theoretical basis for use of melatonin in the treatment of some, but not all CRSDs. Clinical data suggests that melatonin is effective for DSPD, particularly in children, though the size of the phase advance reported is quite variable across the studies and amongst the subjects in the individual studies; responder analysis appears warranted. Appropriately timed exposure to bright light has also shown potential in the treatment of DSPD⁹⁸, though its efficacy compared to melatonin is unclear.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Melatonin has been found to improve DSPD and several other sleep-wake rhythm disturbances in children, including some related to developmental disorders, such as ADHD, autism spectrum disorder, and intellectual disability. Melatonin decreases SOL and increases TST, but has no clear effect on number of night awakenings. Although melatonin has not been adequately compared with other treatments for such disorders, and the long-term safety of melatonin in children and adolescents has not been systematically studied, it is being increasingly used in the attempt to treat children and adolescents with more serious / long-term sleep problems.

OVERVIEW OF SAFETY

Summary of non-clinical safety data for melatonin

The following is a summary of the non-clinical safety data for melatonin presented in [REDACTED]. The term 'animal' refers to mammals other than humans.

Melatonin has very low acute toxicity on administration of single oral doses. LD₅₀ values of 930 mg/kg and 3200 mg/kg have been reported for the mouse and rat, respectively; the recommended doses (3 or 6 mg daily) [REDACTED] product are equivalent to 0.05 – 0.1 mg/kg (for a 60 kg human).

Long-term exposure (in some studies until natural death) of adult rodents (mice, rats) to relatively low oral doses of melatonin has not been clearly associated with adverse effects, though systematic safety studies have not been performed, and data for non-rodent animals are limited. Longer-term exposure of juvenile rodents to melatonin is associated with delayed sexual development, attributable to the inhibitory role of melatonin (i.e. a high endogenous level) on sexual development and annual gonadal hypertrophy in this seasonally-breeding⁹⁹ group of mammals (this issue is addressed in more detail below).

A full battery of *in vitro* and *in vivo* genotoxicity tests have consistently found no evidence that melatonin is genotoxic (neither mutagenic nor clastogenic). A single study reported that very high exposure to melatonin in several *in vitro* test systems induced DNA adducts of uncertain consequence for carcinogenic risk. The primary metabolite of melatonin in humans, 6-hydroxymelatonin, tested negative in the Ames test. [REDACTED]

[REDACTED] o-gonadotrophic or anti-gonadotrophic depending on season.
In the wild, rodents are generally season breeders.

[REDACTED]

[REDACTED]

As melatonin modulates annual gonadal hypertrophy¹⁰² in seasonally-breeding animals, a potential adverse effect of exogenous melatonin on fertility is possible. Exposure of female rats to large s.c. doses of melatonin (starting on Day 1 of pregnancy) and ewes to s.c. melatonin before and for 5 days after mating did not affect pregnancy rates, though the literature data are inadequate to permit evaluation of the effect of oral melatonin on the fertility of female animals, and essentially no fertility data is available for male animals. Administration to rats of oral dose of melatonin up to 200 mg/kg/d during days 6 – 19 of gestation did not affect prenatal survival, fetal body weight, or incidences of fetal malformations and variations.

Oral and s.c. administration of melatonin to pregnant rats generally had no effect on the general development of their male and female offspring but delayed their sexual maturation. Administration s.c. of melatonin to female palm squirrels during pregnancy and post-partum reduced reproductive organ weights and delayed sexual maturation of male and female offspring. These data indicate that exogenous melatonin crosses the placenta and is secreted in milk, and that exposure via these routes may influence the ontogeny and activation of the hypothalamic-pituitary-gonadal axis. However as the wild rat and palm squirrel are seasonal breeders the implications of these findings for humans are uncertain.

[REDACTED]

The above issues are considered in relevant sections of the *Overview of safety*.

General clinical safety of melatonin

Safety information summarised in the following sections indicates that short-term use (defined as 'days') and immediate-term use (defined as 'weeks-to-months') use of exogenous melatonin is generally safe in adult men and women. Safety data from studies of melatonin for jet-lag ([Section 2.5.5.3 Safety in jet-lag](#)), in other disorders ([Section 2.5.5.4 Safety in other clinical studies](#)), and in safety studies and reviews ([Section 2.5.5.5 Safety studies and reviews addressing safety](#)) indicates that adverse events reported most commonly are sleepiness / drowsiness, headache, dizziness, and nausea, though their frequency is low and often comparable to that in subjects receiving placebo. No serious adverse effects were clearly associated with ingestion of typical therapeutic doses of melatonin in the individual studies, and this is supported by reviews addressing specific and general aspects of melatonin safety (e.g. [REDACTED] [REDACTED] considered short-term ingestion of even extreme doses of melatonin by adults in general to be safe, with the above adverse effects the most common signs and symptoms of overdose).

Data for long-term use (defined as 'years') of melatonin by adults are limited; such data is available for children and adolescents, though specifically designed long-term safety studies are lacking for adults and persons under 18 years. The lack of long-term safety data is a particular concern for children and adolescents. While studies to date have not confirmed any specific safety concerns in persons under 18 years, knowledge of the manner in which endogenous melatonin level modulates (activates or suppresses) the hypothalamic-pituitary-gonadal axis in mammals, and animal studies showing that *in utero* and post-partum exposure to melatonin can delay sexual development and potentially affect reproduction, raise the possibility of comparable effects in humans. These potential actions of exogenous melatonin were addressed in [Section 2.5.3.2.3 Secondary pharmacodynamic and safety pharmacology](#); actual endocrinological adverse effects of exogenous melatonin are addressed in [Section 2.5.5.6.1. Endocrinological adverse effects](#). Since no jet-lag studies have been performed in children/adolescents/pregnant-/lactating women), the Applicant's product is not recommended in persons under 18 years or in pregnant or lactating women, or women or men planning a pregnancy.

Issues in addition to endocrinological adverse effects and long-term safety addressed in [Section 2.5.5.6 Specific safety issues](#) include the potential for melatonin to transiently impair glycaemic control when taken in close proximity to a meal, and the lack of effect of exogenous melatonin on the amplitude¹⁰³ of endogenous plasma melatonin.

Issues in addition to overdose, safety during pregnancy and lactation, and in children and adolescents addressed in [Section 2.5.5.9 Safety in special groups and situations](#) include lack of specific concerns related to elderly users, and to tolerance, dependence and withdrawal; the potential for hepatic- and renal impairment to reduce, respectively, the metabolism of melatonin and excretion of melatonin metabolites; and the potential for melatonin to increase risk of seizures and to transiently affect ability to drive and operate machines.

In summary, most of the 10 jet-lag studies did not collect / report adverse events in a systematic manner. Overall, only occasional serious or potentially serious adverse events were reported, though the causal role of melatonin was generally not assessed. The adverse events reported were generally comparable in nature and frequency in the melatonin and placebo groups, though transient drowsiness / sleepiness was more common with melatonin. In relation to the indication and recommended timing of intake (at bedtime) of the Applicant's product, transient drowsiness is considered a beneficial action

rather than an adverse effect. The finding that drowsiness, and possibly also headache and dizziness / disorientation, are the most common (though still only occasional) adverse effects reported when melatonin is taken on a short-term basis to treat jet-lag is in agreement with safety data for melatonin reported in other clinical studies ([Section 2.5.5.4](#)), in safety studies and reviews addressing safety ([Section 2.5.5.5](#)), and post-marketing data ([Section 2.5.5.7](#)).

Safety in other clinical studies

Primary sleep disorders

A crossover RCT [REDACTED] in which 14 adult men and women (mean age ~ 51 years) with reduced REM sleep duration ingested 3 mg IR melatonin or placebo at bedtime for 4 weeks found no adverse effect of melatonin on any efficacy parameter; no side effects were reported.

A RCT [REDACTED] in which 62 children (6 – 12 years) with idiopathic chronic sleep-onset insomnia ingested 5 mg IR melatonin or placebo at 19:00 hr for 4 weeks found no adverse effect of melatonin on any efficacy parameter. No subjects withdrew from the study due to adverse events, and no serious adverse events were reported. After first intake of melatonin, 7 children reported one or more of the following symptoms: a cold feeling¹⁰⁶, decrease in appetite, dizziness, and impaired mood. After first intake of placebo, 3 children reported one or more of the following symptoms: headache, nausea, dizziness, and increased appetite. These possible adverse events subsided within 3 days of starting melatonin or placebo.

A retrospective study [REDACTED] of longer-term treatment of 33 adolescents (10 – 18 years) with Delayed Sleep Phase Disorder (DSPS) with 3 – 6 mg (mean 5 mg) melatonin taken 2 h before desired bedtime for a mean of 6 months (range 1 – 16 months) found that melatonin had not adversely affected any efficacy parameter. No adverse effects had been reported spontaneously or at follow-up visits scheduled every 1 – 3 months. Fifteen of the subjects had ADHD; the safety of melatonin in these patients was comparable to that in the subjects without ADHD.

A systematic review and meta-analysis [REDACTED] that examined the efficacy and safety of exogenous melatonin for primary sleep disorders, primarily insomnia and DSPD included 10 RCTs rated of good quality and involving ~ 220 subjects in a safety

analysis. 7 of the studies involved a dose of 4 or 5 mg, with melatonin administered for at least 3 weeks in 8 of the studies. There were few reports of adverse events during melatonin administration; the most commonly reported were headache (13 events), dizziness (10 events), nausea (3 events), and drowsiness (3 events). For each symptom, there was no significant difference in frequency between melatonin and placebo. This result did not change by type of sleep disorder, dose or formulation of melatonin, duration of treatment, gender, age, use of concurrent medication, study design or quality score, and allocation concealment score.

A meta-analysis [REDACTED] of the efficacy and safety of exogenous melatonin in DSPD that included 5 RCTs including 91 adults, and 4 RCTs including 226 children noted that 4 of the 9 studies did not report any adverse events. In 4 of the studies, ~ 7% of subjects experienced headaches during melatonin treatment, though in 1 study headache was reported in the placebo group only. Other adverse events during melatonin treatment, but not placebo treatment, were feeling cold, dizziness, mood dip, and decreased appetite, though these events were primarily reported in a single study that did not state their frequency. Elevated alkaline phosphatase level was observed in 1 subject on melatonin, though the elevation was almost reversed after 20 weeks of continued melatonin treatment. 1 subject developed a mild case of generalised epilepsy 4 months after having started melatonin (the potential for melatonin to exacerbate or initiate epilepsy is addressed in [Section 2.5.5.9.5 Epilepsy](#) (Safety in special groups and situations)).

Secondary sleep disorders

A RCT [REDACTED] in which 157 patients (mean $\pm$ SD age 77.4 ± 8.9 years; 56.1% women) with Alzheimer's disease and sleep disturbances received 2.5 mg melatonin (slow release), 10 mg melatonin (probably IR) or placebo 1 h before habitual for bedtime for 2 months found that melatonin did not adversely affect any efficacy parameter. There were no differences in the mean number, severity, seriousness, or relatedness ratings of spontaneously reported adverse events in the 3 treatment groups. None of the adverse events reported were considered definitely related to the study medication. All the named groupings¹⁰⁷ of adverse events reported in the 2 melatonin groups were also reported in the placebo group.

A crossover RCT [REDACTED] in which 23 children and adolescents (6 – 14 years) with ADHD and initial insomnia ingested 5 mg melatonin ('short-acting') or placebo 20 minutes before bedtime for 30 days found no adverse effect of melatonin on any efficacy parameter. 20% and 23% of the adverse events (no further details) reported occurred during melatonin or placebo treatment, respectively. One event (a migraine) was categorised as severe. There were no serious adverse events. None of the adverse events were considered causally related to the study interventions.

A systematic review and meta-analysis [REDACTED] that examined the efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction included 7 studies of secondary sleep disorders rated of good quality and involving 164 subjects, and 10 studies of sleep restriction (due to shift-work or jet-lag) rated of good quality and involving 487 subjects, in a safety analyses. In both analyses, the most commonly reported adverse events were headache, dizziness,

[REDACTED]

nausea, and drowsiness; the occurrence of each symptom did not differ significantly for melatonin or placebo. Thus, 17 clinical trials involving 651 participants showed no evidence of adverse effects of melatonin with short-term (< 3 months) use.

A systematic review and meta-analysis [REDACTED] that examined the efficacy and safety of exogenous melatonin for treating sleep problems in individuals with intellectual disabilities included 9 RCTs involving 183 subjects. Typically melatonin doses were 2.5 – 5 mg (though up to 9 mg was given) administered for 2 – 4 weeks. Specific reports on adverse effects were given in 4 of the 9 studies; they were considered minor, and their incidence comparable in the melatonin and placebo groups. Two of the 9 studies reported that no significant adverse effects were observed, while adverse effects were not addressed in the 3 remaining studies, suggesting serious effects were not observed.

Other disorders and situations

A crossover RCT [REDACTED] that studied the effect of 3 mg IR melatonin or placebo taken before bedtime for 11 – 12 days by 45 paediatric residents (29 women, 16 men; mean age 29 years) after working a night-shift found that melatonin did not adversely affect any efficacy parameter. Subjects were required to complete (on a daily basis) an adverse events log that covered general symptoms, gastrointestinal symptoms, excessive sleepiness, and other symptoms. The number of subjects reporting symptoms while on melatonin or placebo were comparable¹⁰⁸. There were no significant differences in the number of days with each symptoms for melatonin compared to placebo. None of the adverse effects were described as serious and melatonin was considered well-tolerated.

A RCT [REDACTED] in which 121 patients scheduled for elective ambulatory laparoscopic cholecystectomy ingested 5 mg IR melatonin or placebo for 3 nights after surgery found nausea, tiredness, and dizziness to be the most commonly reported side effects in the 2 treatment groups. The number and type of side effects reported was not considered to differ in the 2 groups.

A RCT [REDACTED] in which the effect of 3 mg melatonin or placebo ingested 2 h before bedtime for 4 weeks on sleep and asthma were examined in 22 women (mean ($\pm$ SD) age 29.7 ± 7.7 years) with asthma found no adverse effect of melatonin on any efficacy parameter.

[REDACTED] summarised in [Section 2.5.5.5.2 Reviews addressing melatonin safety](#). It is likely that sleepiness / drowsiness is associated with melatonin treatment, particularly in younger children, though this effect is not considered adverse in relation to the proposed indication for the Applicant's product. Overall, safety data from studies other than jet-lag are not considered to raise any new safety concerns.

[REDACTED]

[REDACTED]

While safety data for oral melatonin have been collected from a large number of clinical studies, only 2 published studies were identified that were specifically designed as safety studies. The study of [REDACTED] is considered the most relevant as it involved intake of 10 mg melatonin for 28 days, though it involved men only. The second study [REDACTED] involved ingestion of a single, very high dose (50 mg/kg; equivalent to 3000 mg for a 60 kg person) prior to an operation.

[REDACTED] randomised male volunteers (29 ± 1 years) to 10 mg melatonin (probably IR) (n = 30) or placebo (n = 10) taken at 22:00 hr for 28 days in a double-blind trial. Laboratory measurements included blood chemistry¹⁰⁹, complete blood count, urinalysis, selected hormones (T_3 , T_4 , TSH, LH/FSH, cortisol), and melatonin concentration. Polysomnography (PSG) was carried out, and the Epworth Somnolence Scale (ESS) and a sleep diary were applied (in addition to the routine laboratory parameters referred to above) at each of 5, weekly visits. None of the above parameters were adversely affected in the melatonin group. The subjects were also asked about possible side effects that appeared during treatment. The number of subjects reporting somnolence (57% vs. 60%) or headache (47% vs. 30%) did not differ significantly between the melatonin group and control group, respectively. Figure 1 of the study report indicates that the following side effects were reported by the melatonin and placebo subjects, respectively: fatigue (3 vs. 1), tremor (2 vs. 0), cognitive alteration (2 vs. 2), pyrosis (1 vs. 0), depression (1 vs. 1), irritability (1 vs. 0), illness (2 vs. 0), torpor (0 vs. 1), tinnitus (0 vs. 1). Taking into account the number of subjects in each group, the number of subjects reporting each symptom is considered comparable in the melatonin and control groups.

A pilot RCT [REDACTED] evaluated the safety of single oral dose of 50 mg/kg IR melatonin or placebo ingested before applying general anaesthesia to 48 patients (20 women, 28 men; 57 ± 11 years) undergoing major liver resection. Biochemical panel, hematology, and liver tests were measured on the day of operation and daily during the postoperative study period of 7 days. No statistically significant difference was observed between the treatment groups for any of the laboratory parameters at any given time point. Melatonin treatment tended to lower postoperative transaminases over the study period. Eleven adverse events (non serious) occurred in 8 patients receiving melatonin, while 18 adverse events occurred in 7 patients receiving placebo; none were considered treatment-related and all patients with adverse events completed the study.

Although not specifically designed as a safety study, a RCT [REDACTED] that measured routine blood chemistry and haematology parameters, and selected hormones in 22 subjects (60.1 ± 9.5 years; 16 women) before and after 6 months intake of 3 mg of melatonin (probably IR) 30 minutes before bedtime did not observe any adverse changes

[REDACTED]

to these parameters (see [Table 2 of the study report](#)), and no adverse effects attributed to melatonin were reported.

[REDACTED]

A review [REDACTED] of adverse effects reported by 2337 adults taking 1 – 10 mg oral melatonin, or placebo, for a minimum of 3 days in 50 RCTs found little evidence of adverse effects, and essentially no evidence of serious adverse effects in healthy persons and in patients with a range of medical conditions. The review addressed both objective and subjective effects. The studies generally reported data for safety parameters such as haematology and blood chemistry as group means, though it is normal practice for any significant deviations from the reference range observed in individual subjects to be mentioned in study reports.

A review [REDACTED] of 35 clinical trials of the effectiveness of melatonin for promoting sleep noted that 15 of the trial reports included information on adverse events, with no serious adverse events reported. An additional study report stated that adverse events occurred, but did not describe them, and a further 2 study reports stated that no adverse events occurred. The most common adverse events were headache and somnolence. Palpitations and abdominal pain were each reported in 2 studies. The remaining adverse events were reported infrequently, each occurring in only 1 of the multiple studies, and comprised nasopharyngitis, arthralgia, tachycardia, dizziness, nausea, vomiting, nightmares, difficulty swallowing and breathing, hypnotic activity, heavy head, heartburn, flatulence, swelling of arms / legs, sweating / hot flush, exanthema, sleeping difficulties, depression, and sleep walking.

A recent review of the safety of melatonin [REDACTED] concluded that, in general, clinical data (supported by animal data) indicate that short-term (defined as 'days') use of melatonin is safe, even in extreme doses, with only mild adverse effects such as sleepiness, headache, dizziness, and nausea having been reported. Immediate-term and long-term use of melatonin (defined as 'weeks-to-months' and 'years', respectively) was also only associated with minor adverse effects. It was considered that no studies have indicated that melatonin induces serious adverse effects, but that long-term safety in children and adolescents requires further investigation. However, it should be noted that a recent review [REDACTED] concluded that melatonin treatment in children/adolescents can be considered safe, provided administration is properly timed and the minimal effective dose is used. Due to lack of human studies, it was recommended that pregnant and breast-feeding women should not take exogenous melatonin.

Similar to the above, the review [REDACTED] described orally taken melatonin to generally be safe with "...few adverse events that cannot be easily avoided or managed in most populations...". However, it did raise the concern for the use of co-medication of melatonin in hypertensive patients treated with anti-hypertensives, especially calcium channel blockers (discussed in [section 2.5.3.2.3.2 Cardiovascular function](#)). It is noteworthy that the two studies observing these effects exposed their patients to melatonin treatment for at least 4 weeks, and that none of the studies, including a third study treating such patients for 1 year, observed significant adverse events. Hence, it seems unlikely that short term treatment for which the Applicants product is intended has any significant effect on this patient group.

[REDACTED] lists (alphabetically) the following adverse effects for melatonin:

Frequency	Adverse effects
Uncommon	abdominal pain, abnormal dreams, anxiety, chest pain, dizziness, dry mouth, dry skin, dyspepsia, glycosuria, headache, hypertension, irritability, malaise, mouth ulceration, nausea, nervousness, proteinuria, pruritus, rash, restlessness, weight gain
Rare	aggression, arthritis, electrolyte disturbances, flatulence, gastritis, haematuria, halitosis, hot flushes, hypertriglyceridaemia, impaired memory, increased libido, lacrimation, leukopenia, mood changes, muscle spasm, nail disorder, palpitation, paraesthesia, polyuria, priapism, prostatitis, restless legs syndrome, salivation, syncope, thirst, thrombocytopenia, visual disturbances, vomiting
Not known	galactorrhoea, mouth oedema, tongue oedema

[REDACTED]

[REDACTED]

[REDACTED] *Immune system adverse effects*

Information presented in [REDACTED] (Secondary pharmacodynamics and safety pharmacology) addresses the role of endogenous melatonin in modulation of immune system function, and the potential for exogenous melatonin to affect the immune system in both a positive and negative manner. Studies involving ingestion of doses of melatonin comparable to or greater than the recommended doses for the Applicant's product for periods of up to 6 months were not found to have adverse effects on white blood cell counts or other immune system parameters, nor to be associated with increased incidences of adverse effects involving the immune system.

Several relevant case reports were identified in the literature. [REDACTED] reported a temporal relationship between melatonin use and the development of autoimmune hepatitis. [REDACTED] described exacerbation of symptoms of Crohn's disease when melatonin was taken in addition to corticosteroids and salicylazosulfapyridine. [REDACTED] described exacerbation of well-controlled ulcerative colitis following 2 months intake of an unidentified melatonin 3 mg product at bedtime that resolved 24 – 48 h after seponation of melatonin. The role of melatonin in the events described in the case reports is generally uncertain. A case report of autoimmune hepatitis that developed in association with use of the melatonin agonist, ramelteon is also considered relevant [REDACTED]

[REDACTED]

110 While the case reports in this and comparable Competent Authority databases may not be evaluated for causality, they can contribute to assessment of the frequency of adverse events.

Although the relevant data is limited, the above case reports, plus knowledge on the capacity of melatonin to modulate immune system function, have led to the inclusion of the text in [Section 4.4 of the proposed SmPC](#) stating that occasional case reports have described exacerbation of an autoimmune disease in patients taking melatonin, that there are no data regarding use of the Applicant's product in patients with autoimmune diseases, and that its use is not recommended in patients with autoimmune diseases.

Sexual development adverse effects

Information presented in [Section 2.5.3.2.3.5 Sexual development](#) (Secondary pharmacodynamics and safety pharmacology) addresses the role of endogenous melatonin in modulation of sexual development, and the potential for exogenous melatonin to adversely affect sexual development. Data from 1 long-term study in pre-pubertal / pubertal children [REDACTED] were presented, though this study was not specifically designed as a safety study. Relevant published data are limited, although a recent review [REDACTED] identified 4 long-term studies (including [REDACTED] evaluating melatonin-treatment in children/adolescents, and concluded that melatonin-treatment could be considered safe, provided administration is properly timed and minimal effective dose is used. [REDACTED]

[REDACTED]

[REDACTED]

As the safety (and efficacy) of the product has not been established for the treatment of jet-lag in children and adolescents aged 0 – 18 years it should not be used in children and adolescents for this indication (as given in the SmPC). Please note that the safety of melatonin treatment in children is addressed in more detail in an addendum to this clinical overview (see [clinical addendum](#)).

[REDACTED]

Information presented in [Section 2.5.3.2.3.1 Metabolic function](#) (Secondary pharmacodynamics and safety pharmacology) addressed the role of endogenous melatonin in glucose homeostasis. Published data for oral melatonin were not considered to suggest that the Applicant's product is likely to have any long-term adverse effects glycaemic control, though limited data indicate that melatonin taken in close proximity to meals might cause transient impairment, a conclusion which is in line with that of a recent review on the subject [REDACTED]

[REDACTED]

Although the available data are limited, the finding that oral melatonin can transiently impair glycaemic control when taken immediately prior to an oral glucose tolerance test

has led to the inclusion of text in [Sections 4.2 and 4.4 of the proposed SmPC](#) noting that intake of melatonin with carbohydrate-rich meals may impair blood glucose control for several hours, and text in Section 4.2 and 4.4 recommending that the product should be taken at least 2 h before and at least 2 h after a meal, and ideally at least 3 h after a meal by persons with significantly impaired glucose tolerance or diabetes. [Section 4.8 of the proposed SmPC](#) lists *hyperglycaemia* (SOC *Metabolism and nutrition disorders*; Frequency *not known*).

[REDACTED]

[REDACTED]

[REDACTED] found 3 mg melatonin (probably IR) ingested 30 minutes before bedtime for 6 months to have no effect on routine blood biochemical tests (including measures of glycaemic control, and liver and kidney function) or differential WBC counts in 22 subjects (60.1 ± 9.5 years; 16 women) with insomnia (20 taking a benzodiazepine). Serum concentrations of estradiol and FSH in the women, and serum concentrations of prolactin and TSH in the same 16 women plus 6 men were unchanged. No side effects attributed to melatonin were reported. These data are in good agreement with those of [REDACTED] following ingestion of 10 mg melatonin (probably IR) daily for 28 days to healthy younger men (see [Section 2.5.5.5.1 Safety studies](#)).

Several clinical studies (e.g. [A \[REDACTED\]](#)) that administered oral melatonin to children and/or adolescents for periods of up to 3 years have reported safety data, though none were specifically designed as safety studies. Serious adverse effects or other important safety signals were not observed, though the safety data comprised primarily adverse events reported by patients or their parents / caregivers, or collected on questioning by the investigators. None of the studies systematically measured routine blood chemistry or haematology parameters. The lack of data for endocrine parameters, and for reproductive issues in general, is of concern considering the apparent role of endogenous melatonin – more specifically the gradual fall in melatonin level around 9 – 10 years of age – in the cascade of events preceding the awakening of the hypothalamic-pituitary-gonadal axis at puberty ([REDACTED]).

A review of the safety of melatonin [REDACTED] considered intermediate use (defined as weeks-to-months) to be associated only with minor adverse effects in children and adults, but that its long-term safety requires further investigation.

It is also considered relevant to mention that a study [REDACTED] of the melatonin-receptor agonist, ramelteon, in which 122 subjects (69 women, 52 men; mean age 34 years) with chronic insomnia were randomised to ramelteon 16 mg, or placebo, nightly for 6 months found no consistent statistically significant effects on measures¹¹¹ of thyroid function (TSH, total T₃, total- and free T₄), adrenal function (cortisol, ACTH), or reproductive endocrine function (LH, FSH, estradiol (women), total- and free testosterone (men)); prolactin concentration in women showed a mild, transient increase though no clinical effects of elevated prolactin were reported. Average menstrual cycle length, duration of menses, and ovulation probability were unaffected.

[REDACTED]

[REDACTED]

[REDACTED]

The capacity for exogenous melatonin to advance or delay the onset of endogenous melatonin synthesis and the subsequent peak plasma level is the mechanism of action that underlies the primary pharmacodynamic effect of melatonin in relation to this application (see [Section 2.5.3.2.2 Primary pharmacodynamics](#)).

[REDACTED]

None of the studies in [Section 2.5.5 Overview of Safety](#) suggested that exogenous melatonin may have an adverse effect on quantitative aspects of endogenous melatonin secretion.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] activities.

Autoimmune diseases

Two reviews and 3 case reports considered relevant were summarised in the PSURs (they, and others, are summarised in [REDACTED]). A single relevant case report had been received for the MAH's product. Although the data available for evaluating the potential for melatonin to exacerbate or induce autoimmune diseases were limited, inclusion of an appropriate warning in [Section 4.4 of the product's SmPC](#) was proposed and was accepted by the Competent Authority. An expanded warning is included in [Section 4.4 of the proposed SmPC](#) for the Applicant's product (see [Immune system adverse effects](#)).

Seizures

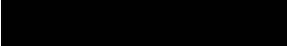
Eight studies, 1 review, and 1 case report considered relevant were summarised in the PSURs (several of the studies, the review, and a more recent review, are summarised in [REDACTED] [Epilepsy](#)). The case report is that of [REDACTED] referred to in the introduction to this section. The majority of the data is for paediatric patients, a population in which the use of the MAH's product is not recommended. Although the data were equivocal, inclusion of an appropriate warning in [Section 4.4 of the product's SmPC](#) was proposed and was partly accepted by the Competent Authority, though it was removed by the Authority during a later update. The MAH's proposal to list seizure (with unknown frequency) in [Section 4.8](#) was not accepted. Although data indicating that melatonin may induce or exacerbate seizures are limited, a warning comparable to that proposed in the PSURs is included in [Section 4.4 of the proposed SmPC](#) for the Applicant's product (see [Section 2.5.5.9.5 Epilepsy](#)).

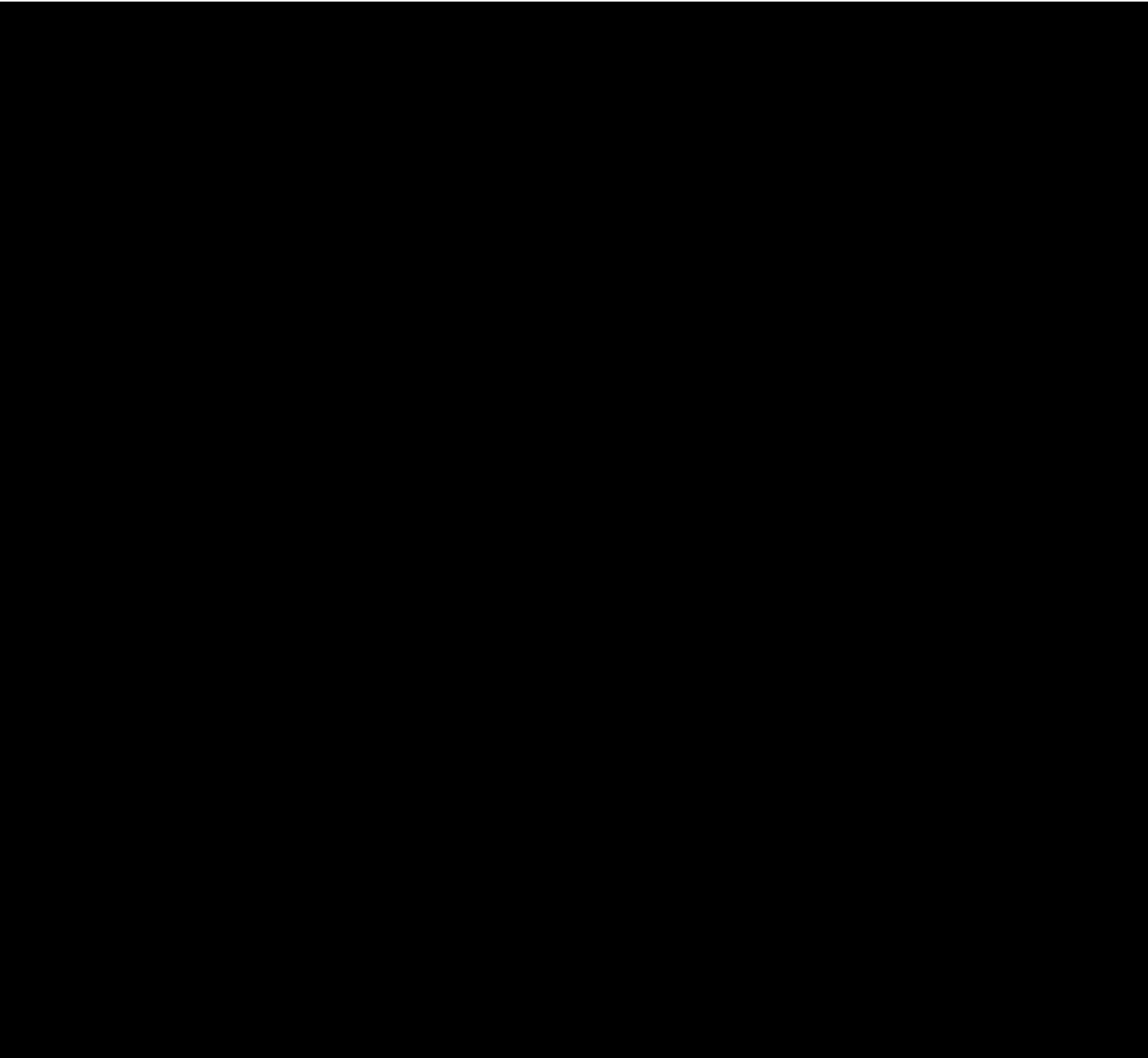
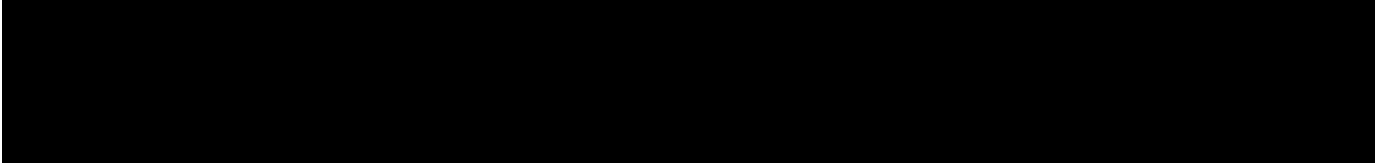
Loss of response in slow metabolisers

A clinical study considered relevant was summarised in the second PSURs (it is summarised in [REDACTED] [Genotype](#)). No relevant case reports had been received for the MAH's product. The available data were limited, and the MAH noted that the brief (4 – 7 day) treatment period recommended for its product could be expected to limit the potential for loss of response. However, due to the potential for longer periods of use, inclusion of an appropriate warning in [Section 4.4 of the product's SmPC](#) was proposed, though was not accepted by the Competent Authority. Due to the short period of intake (maximum 5 days) in the present Application, the potential for loss of response is not addressed in the proposed SmPC.

In addition to addressing loss of response to melatonin with a basis in genetically reduced capacity for metabolism of melatonin, [PSUR 2](#) also addressed the potential for loss of response in patients with significantly impaired liver function; no specific data were presented, rather the concern was based on the fact that oral melatonin is predominantly metabolised by the liver. Inclusion of an appropriate warning in [Sections 4.2 and 4.4 of the product's SmPC](#) was proposed, though only the former was accepted by the Competent Authority. A revised version of the [Section 4.2](#) text, plus a relevant warning and text in [Sections 4.4 and 5.2](#), are included in the [proposed SmPC](#) for the Applicant's product (see [Hepatic impairment](#)).

Interaction with zolpidem (and related drugs)

A study reporting interaction between melatonin (prolonged release) and zolpidem, and also evaluating the potential for melatonin to potentiate the hypnotic effects of GABA-A receptor modulators, notably benzodiazepine and non-benzodiazepine hypnotics (such as zolpidem), was reviewed in [PSUR 2](#) (this study, and a more relevant study are summarised in [Section 2.5.5.9.12.1 Zolpidem \(and related drugs\)](#)). Although the available data were limited, inclusion of an appropriate warning in Section 4.5 of the product's SmPC was proposed and was accepted by the Competent Authority. A revised version of the warning is included in [Section 4.5 of the proposed SmPC](#) for the Applicant's product (see  [Zolpidem \(and related drugs\)](#)).



[REDACTED]

[REDACTED]

[REDACTED]

Information include in [Section 4.8 Undesirable effects of the proposed SmPC](#) for the Applicant's product:

Summary of the safety profile

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

Tabulated list adverse reactions

The following adverse reactions to melatonin in general have been reported in clinical trails or spontaneous case reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

[REDACTED]

System Organ class	Very common(≥ 1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from available data)
Blood and lymphatic system disorders				leucopenia, thrombocytopenia	
Immune system disorders					hypersensitivity reaction
Metabolism and nutrition disorders				hypertriglycerid-aemia	hyperglycaemia
Psychiatric disorders			irritability, nervousness, restlessness, abnormal dreams, anxiety	mood altered, aggressive behaviour, disorientation, libido increased	
Nervous system disorders		headache, somnolence	dizziness	syncope (fainting), memory impairment, restless legs syndrome, paraesthesia	
Eye disorders				visual acuity reduced, vision blurred, lacrimation increased	
Cardiac disorders				palpitations	
Vascular disorders			hypertension	hot flushes	
Gastrointestinal disorders			abdominal pain, upper abdominal pain, dyspepsia, oral ulcers, dry mouth, nausea	vomiting, flatulence, salivary hyper-secretion, halitosis, gastritis	
Skin and subcutaneous tissue disorders			pruritus, rash, dry skin	nail disorder	tongue edema, edema of the oral mucosa
Musculoskeletal and connective tissue disorders				arthritis, muscle spasms	
Renal and urinary disorders			glycosuria, proteinuria	polyuria, haematuria	
Reproductive system and breast disorders				priapism, prostatitis	galactorrhoea
General disorders and administration			chest pain, malaise	thirst	

System Organ class	Very common(≥ 1/10)	Common(≥1/100 to <1/10)	Uncommon(≥1/1,000 to <1/100)	Rare(≥1/10,000 to <1/1,000)	Not known (cannot be estimated from available data)
site conditions					
Laboratory and other examinations			weight increased	blood electrolytes abnormal	

Safety in special groups and situations

Elderly

Age (adults) (Pharmacokinetics) notes that the pharmacokinetics of oral melatonin is generally comparable in younger and older adults. In particular, rapid plasma elimination half-life ($T_{1/2}$; ~ 45 minutes) is not prolonged in the elderly in general, limiting the potential for adverse effects due to accumulation of melatonin. Thus the PK of melatonin in the elderly is not considered to have implications for the safety of the Applicant's product in this patient group.

The 10 pivotal jet-lag studies, which typically enrolled subjects in their mid-20s to mid-60s (no study enrolled persons or over 68 years) do not suggest any safety problems in older compared to younger adults, though the safety data collected was essentially restricted to investigator-driven and spontaneous reporting of adverse events (see [REDACTED]).

A number of the other clinical studies summarised in [Section 2.5.5 Overview of safety](#) included or involved elderly subjects. [REDACTED] (summarised in [Safety in other studies](#)) found that ingestion of 2.5 mg melatonin (slow release), 10 mg melatonin (probably IR) or placebo 1 hour before habitual bedtime for 2 months by 157 subjects (56% women) with a mean age of ~ 77 years did not have an adverse effect on any efficacy parameter, and that there were no differences in the mean number, severity, seriousness, or relatedness ratings of spontaneously reported adverse events in the 3 treatment groups. [REDACTED] summarised in [Long-term](#) [REDACTED] found ingestion of 3 mg melatonin (probably IR) 30 minutes before bedtime for 6 months by 22 subjects (73% women) with a mean age of ~ 60 years to have no effect on routine blood biochemical tests, differential WBC, or selected hormones, and no side effects attributed to melatonin were reported.

Safety reviews of melatonin summarised in [REDACTED] [Reviews addressing melatonin safety](#) have not raised relevant concerns.

Case reports in which adverse effects were linked to patient (old) age have not been identified in the literature, and no relevant case reports were received for a 3 mg melatonin tablet (IR) for which the Applicant was MAH in Hungary from July 2003 until January 2017.

In summary, no concerns regarding use in the elderly are considered evident, and no related safety information is included in the proposed SmPC.

Hepatic impairment

Hepatic impairment (Pharmacokinetics) notes that hepatic impairment can reduce the clearance of exogenous melatonin, though the relationship between the nature / degree of hepatic impairment and the extent of the reduction in melatonin metabolism is unclear, and that there is no relevant data for the Applicant's product. Consequently, there is considered to be insufficient data to permit alternative dosing recommendations for any degree of hepatic impairment. The available data is, however, considered sufficient to support inclusion of text in [Sections 4.2 and 4.4 of the proposed SmPC](#) recommending that the product is not used by patients with severe hepatic impairment, with background information included under the heading *Hepatic impairment* (Special populations) of [REDACTED]

Hepatic impairment can potentially result in incomplete next-morning clearance of typical therapeutic doses (~ 2 – 6 mg) of IR melatonin taken at bedtime the previous evening. As plasma endogenous melatonin level is at its lowest between early morning and early evening, such a situation can be expected to result in disturbance of activities modulated by the circadian rhythmicity of melatonin; symptoms such as early morning sleepiness and disturbed sleep / wake pattern can be predicted. However, studies addressing the effect of hepatic impairment on the safety of exogenous melatonin were not identified in the literature. As hepatic impairment has a higher prevalence in the elderly, it is considered relevant to note that a study ([REDACTED]) in which 157 subjects with a mean age of 77 years took 1 of 2 melatonin interventions or placebo 1 hour before habitual bedtime for 2 months did not observe treatment-related differences in spontaneously reported adverse events or any safety parameter measured.

Reviews of melatonin summarised in [REDACTED] [Reviews addressing melatonin safety](#) did not present any specific safety data of relevance. [REDACTED]

Renal impairment

Renal impairment (Pharmacokinetics) notes that as less than ~ 1% of exogenous melatonin is excreted untransformed in the urine, renal impairment is not expected to significantly increase absolute plasma melatonin concentration. However, supporting data are limited and indirect, and do not address the relationship between the

nature / degree of renal impairment and the extent of the reduction in melatonin excretion, and there is no relevant data for the Applicant's product. Consequently, there is considered to be insufficient data to permit alternative dosing recommendations for any degree of renal impairment. The available data is, however, considered sufficient to support inclusion of text in [Sections 4.2 and 4.4 of the proposed SmPC](#) recommending that the product is not used by patients with severe renal impairment, with background information included under the heading *Renal impairment* (Special populations) of [REDACTED]

While less than ~ 1% of exogenous melatonin is excreted untransformed in the urine, its metabolites are predominantly excreted via the urine, and it can be predicted that their plasma levels will be elevated in patients with more advanced renal impairment compared to healthy subjects following ingestion of melatonin. Studies addressing the effect of renal impairment on the safety of exogenous melatonin (the accumulation of melatonin and/or its metabolites) were not identified in the literature. As renal impairment has a higher prevalence in the elderly, it is considered relevant to note that a study [REDACTED] in which 157 subjects with a mean age of 77 years took 1 of 2 melatonin interventions or placebo 1 hour before habitual for bedtime for 2 months did not observe and treatment-related differences in spontaneously reported adverse events or any safety parameter measured.

Reviews of melatonin summarised in [REDACTED] [Reviews addressing melatonin safety](#) did not present any specific safety data of relevance. [REDACTED]

In summary, the text regarding renal impairment included in [Sections 4.2 and 4.4 of the proposed SmPC](#) is primarily based on the potential safety implications of the available (limited) PK data, though the text in [Section 4.4](#) notes that only limited data are available on the safety of melatonin in patients with renal impairment.

Genetic factors

[REDACTED] [Race](#) and [REDACTED] [Genotype](#) (Pharmacokinetics) present limited and equivocal data regarding the possible influence of race and genotype on the PK of melatonin. Reduced activity of hepatic CYP1A2, the primary P450 isoenzyme responsible for the metabolism of melatonin, could potentially result in increased exposure. This was not seen in a study in which subjects with the g.-163C>A polymorphism ingested 6 mg IR melatonin, though a single nucleotide polymorphism in the CYP1A2 gene has been associated with slow metabolism of melatonin. As melatonin has a short plasma elimination half-life (~ 45 minutes), and the maximum recommended duration of a treatment period for the Applicant's product is 5 days, the degree of impairment of melatonin metabolism due to race or genotype is considered to be of limited clinical significance.

The 10 pivotal jet-lag studies did not consider race or genetic factors. Reviews of melatonin summarised in [REDACTED] [Reviews addressing melatonin safety](#) have not raised relevant concerns.

In summary, no concerns regarding race genotype are considered evident, and no related safety information is included in the proposed SmPC.

Epilepsy

A number of clinical trials have examined the efficacy of oral melatonin for sleep disorders associated with neurological and psychiatric disorders, with the majority involving children and adolescents. As such conditions can be associated with an increased risk of seizures, the studies in question have typically monitored the potential for melatonin to exacerbate seizures or to induce seizures in those with no previous history. Several relevant trials and reviews are summarised below.

found no suggestion that long-term intake of melatonin activated an epileptic event in 19 paediatric patients with a seizure disorder. A study in which 51 children and young adults with intellectual disability were treated with melatonin or placebo for 4 weeks observed no changes in seizure frequency. A 3.7-year follow-up study of 101 children with ADHD who had previously been given 3 – 6 mg melatonin for 4 weeks found none to have developed epilepsy, a findings considered consistent with literature data indicating no clear pro-convulsive action of melatonin.

A review of melatonin for sleep disorders associated with intellectual disability noted that while a few studies have reported worsening of or development of seizures after initiation of melatonin, a number of others have not found melatonin to have such effects and that it may actually have beneficial effects on seizure. A recent review of the potential for melatonin to affect epileptic seizures identified 3 RCTs of which 2 showed no overall worsening or improvement in seizures, and the third a statistically significant reduction in seizures. The open studies identified reported conflicting results.

Based on the above, [Section 4.4 of the proposed SmPC](#) for the Applicant's product notes that melatonin may increase seizure frequency in patients experiencing seizures (e.g. epileptic patients), and that patients suffering from seizures must be informed about this possibility before using the product. Although the product is not recommended in persons under 18 years of age, [Section 4.4](#) also notes that melatonin may promote or increase the incidence of seizures in children and adolescents with multiple neurological defects.

Pregnancy and lactation

Pregnancy

Data reviewed in the [Non-clinical Overview](#) confirm that exogenous melatonin moves rapidly and efficiently across the placenta of non-primate and primate species including humans. A formal developmental toxicity study in rats a developmental toxicity NOAEL of ≥ 200 mg/kg bw/d¹¹⁹. Delayed sexual maturation has been observed in male and female off-spring of rats.

[REDACTED] palm squirrels [REDACTED] exposed to considerably lower levels of melatonin during pregnancy. However, the mammals in which exogenous melatonin has been found to affect (typically delay) sexual maturity and/or annual breeding are – unlike humans – seasonal breeders, i.e. species in which melatonin tends to act as either pro-gonadotrophic or anti-gonadotrophic according to photo-period (duration of daylight).

[Section 2.5.3.2.3.4 Reproductive function](#) (Secondary pharmacodynamics and safety pharmacology) notes that exogenous melatonin readily crosses the human placenta and enters the fetal circulation [REDACTED] though there are no published data on the effect of *in utero* exposure to melatonin on pre- and post-natal development in humans. [REDACTED]

Based on the above information the *Pregnancy* heading of [Section 4.6 of the proposed SmPC](#) includes text noting that there are no or limited amounts or data from the use of melatonin in pregnant women, that animal studies are insufficient with respect to reproductive toxicity (with reference to [Section 5.3](#)), and that the product is not recommended during pregnancy. [Section 5.3](#) includes text noting that after oral and sub-cutaneous administration of large doses of melatonin to pregnant rats, fetal body weight and length tended to be lower, possibly due to maternal toxicity. It also notes that delay in sexual maturation in male and female off-spring of rats and palm squirrels occurred on exposure to melatonin during pregnancy, indicating that exogenous melatonin crosses the placenta and that it may influence the ontogeny and activation of the hypothalamic-pituitary-gonadal axis, though as the wild rat and palm squirrel are seasonal breeders, the implications of these findings for humans are uncertain. Text included under the heading *Distribution* in [Section 5.2 of the proposed SmPC](#) notes that melatonin readily crosses the placenta, and that the melatonin level in umbilical blood of full-term babies closely correlates with, and is only slightly lower (~ 15 – 35%) than, that of their mothers following ingestion of a 3 mg dose.

As essentially no safety information regarding use of melatonin during pregnancy was identified, use during pregnancy is listed as missing information in the product's RMP.

[\[REDACTED\]](#) *Lactation*

Data reviewed in in the [Non-clinical Overview](#) confirm that exogenous melatonin is excreted in milk. Data regarding the extent of excretion of exogenous melatonin in milk were not identified in the literature, though a study of palm squirrels [REDACTED] found the delay in sexual maturation of off-spring of mothers exposed to melatonin during pregnancy and lactation to be greater than in off-spring exposed during pregnancy only, indicating that exogenous melatonin distributed into the milk of this species in a quantity sufficient to affect the sexual maturation of their off-spring.

[\[REDACTED\]](#) [Reproductive function](#) (Secondary pharmacodynamics and safety pharmacology) notes that data for the excretion of exogenous melatonin and eventually also its metabolites in human milk are not available, though as endogenous melatonin is excreted in human milk [REDACTED] it is likely that exogenous melatonin is excreted to at least some extent in human milk. No safety data (including case reports) for clinical exposure to exogenous melatonin via lactation were identified in the literature.

[REDACTED]

Based on the above information, text included under the heading *Lactation* in [Section 4.6 of the proposed SmPC](#) notes that there is insufficiency data on the excretion of melatonin or its metabolites in human milk though it is known that endogenous melatonin is excreted in human milk, that available pharmacodynamic / toxicological data in animals have shown excretion of melatonin / metabolites in milk (with reference to [Section 5.3](#)), that a risk to the suckling child cannot be excluded, and that the product should not be used during breast-feeding. [Section 5.3](#) includes text noting that delay in sexual maturation in male and female off-spring of rats and palm squirrels occurred on exposure to melatonin post-partum, indicating that exogenous melatonin is secreted in milk and that it may influence the ontogeny and activation of the hypothalamic-pituitary-gonadal axis, though as the rat and palm squirrel are seasonal breeders the implications of these findings for humans are uncertain.

As essentially no safety information regarding use of melatonin during lactation was identified, use during lactation is listed as missing information in the product's RMP.

Fertility

As melatonin modulates annual gonadal hypertrophy in seasonally-breeding animals, a potential adverse effect of exogenous melatonin on fertility is possible. In male rats, moderate amounts of exogenous melatonin increase sexual functions, whereas high doses have inhibitory effects in both sexes. Exposure of ewes to s.c. melatonin before and for 5 days after mating did not affect pregnancy rates. The literature is, however, insufficient to permit evaluation of the effect of oral melatonin on animal fertility.

Humans, unlike most mammals, are not seasonal breeders, and thus may be less susceptible to effects of exogenous melatonin. [REDACTED] considered the balance of evidence from clinical studies to suggest that the effect of melatonin on human reproductive processes such as ovulation and fertility is attenuated compared to that in animals. [REDACTED] [Reproductive function](#) (Secondary pharmacodynamics and safety pharmacology) notes that information on the effects of exogenous melatonin on human ova, sperm, and fertility are limited [REDACTED]

[REDACTED]

Based on the above information the *Pregnancy* heading of [Section 4.6 of the proposed SmPC](#) includes text noting that high doses of melatonin and use for longer periods than indicated may compromise fertility in humans, that animal studies are insufficient with respect to effects on fertility (with reference to [Section 5.3](#)), and that the product is not recommended in men and women planning a pregnancy. [Section 5.3](#) does not provide any specific data on effects on fertility.

As essentially no safety information regarding effects of melatonin on fertility was identified, this issue will be considered along with pregnancy as missing information in the product's RMP.

Children and adolescents

The safety of oral melatonin in children and adolescents, and in particular its potential to affect sexual development, is addressed in [Section 2.5.3.2.3.5 Sexual development](#) (Secondary pharmacodynamics and safety pharmacology) and in [Section 2.5.5.6.1.2 Sexual development adverse effects](#) (Specific safety issues), with relevant information¹²⁰ included in the proposed SmPC presented in the latter. The information in the above sections is included in the SmPC. Importantly, an addendum to this overview addresses the safety of melatonin treatment in children in more detail (see [clinical addendum](#)).

Food and alcohol

The ~ 2-fold greater increase in plasma melatonin level expected if the recommended dose of the Applicant's product is taken with food (as opposed to on an empty stomach)¹²¹ is not considered a safety concern. That food appears to have a limited effect on T_{max} and plasma half-life for IR melatonin are also positive efficacy / safety findings, as the rapid rise in plasma melatonin level post-ingestion, and the subsequent efficient elimination of melatonin from the plasma, have implications for the efficacy of the single daily dose of melatonin to re-entrain circadian rhythmicity.

None of the reports of the 10 key jet-lag studies in the [redacted] of melatonin for jet-lag [redacted] state if intake of food was restricted in relation to the scheduled intake of melatonin. Although these studies do not provide any direct data on the influence of food on the safety and efficacy of melatonin, they indicate that melatonin is generally safe when taken at bedtime by travelers unrestricted in relation to timing of meals in-flight or post-flight. Limited data presented in [Section 2.5.5.6.2 Adverse effects on glycaemic control](#) suggest that intake of melatonin with carbohydrate-rich meals may impair blood glucose control for several hours. While the recommended posology reduces the likelihood that the Applicant's product will be taken close to meals, this issue has relevance to persons with significantly impaired glucose tolerance or diabetes.

Text included under the heading *Absorption* in [Section 5.2 of the proposed SmPC](#) for the Applicant's product notes that food is not expected to affect the safety or efficacy of the product, however it is recommended that food is not consumed 2 before or 2 h after intake of melatonin. Relevant text regarding the potential for food to increase plasma exogenous melatonin level, and the possibility that melatonin taken with carbohydrate-rich meals may impair blood glucose control is included in [Sections 4.2 and 4.4](#).

Alcohol

No studies examining the influence on alcohol on the safety of oral melatonin in general, or its safety / efficacy for treatment of jet-lag, were identified in the literature. Several of the 10 key jet-lag studies in the Cochrane Review of melatonin for jet-lag [redacted] (updated 2008) required that alcohol (any alcohol in 2 studies, alcohol intake greater than normal in 2 studies, strong alcohol in 1 study) was avoided in-flight and/or post-flight. As alcohol can impair sleep, cause diuresis (also disturbing sleep due to the

need for toilet visits), potentially worsen certain symptoms of jet-lag (e.g. headache, morning fatigue, concentration), and have a sedative effect when consumed in large quantities, avoidance of alcohol during melatonin treatment is considered prudent. Relevant information is included under the *Posology* heading in [Section 4.2 of the proposed SmPC.](#))

Tolerance, dependence, withdrawal & abuse

Due the short maximum recommended duration (5 days) of an individual treatment period proposed for the Applicant's product, development of tolerance is considered unlikely. Tolerance was not addressed in the vast majority of clinical studies involving adults. A study in which paediatric patients were followed for up to 3.8 years considered there to be no evidence of tolerance with long-term use. Tolerance has not been raised as a safety concern in reviews summarised in [Reviews addressing melatonin safety.](#)

Clinical studies summarised in [Overview of safety](#), and reviews of melatonin summarised in [Reviews addressing melatonin safety.](#), have not raised concerns regarding the potential for dependence. The brief maximum recommended duration (5 days) of an individual treatment period proposed for the Applicant's product contributes to a low risk of dependence.

Clinical studies summarised in [Overview of safety](#), including the 10 pivotal jet-lag studies, and reviews of melatonin summarised in [Reviews addressing melatonin safety.](#) have not raised concerns regarding the potential for withdrawal effects. A study in which 75% of 791 adults (aged 18 – 80 yr) received 2 mg melatonin (prolonged-release) for 26 – 29 weeks found no evidence of withdrawal or rebound effects during a 2-week run-out period.

Clinical studies summarised in [Overview of safety](#), and reviews of melatonin summarised in [Reviews addressing melatonin safety.](#), have not raised concerns regarding the potential for abuse.

Overdose

Overdose may be considered in terms of acute accidental- or deliberate overdose, or prolonged overdose (technically misuse). Data from published clinical trials and cohort studies with doses of melatonin equivalent to mild prolonged overdose, or to significant or extreme¹²² acute overdose, of the Applicant's product reported no or only occasional, mild, self-limiting adverse effects.

A study specifically designed to assess the safety of oral melatonin (10 mg, probably IR), taken once daily at 22:00 hr for 28 days by 30 healthy men (an additional 10 men took placebo) did not observe differences between melatonin and placebo for a broad range of objective or subjective safety parameters¹²³ nor for adverse effects. Headache was reported more frequently in the melatonin group (47% vs. 30%) though the difference was not statistically significant. reported that daily intake of 300 mg melatonin for 4 months by 8 younger women (19 – 37 years) reduced levels of LH, estradiol, and progesterone, but did not affect menstrual bleeding patterns, or result in physical complaints or complaints about altered- sleep or activity patterns, emotional well-being, or mood. The results of all haematological and biochemistry measurement during and after the treatment were normal. A study in which patients undergoing liver resection were given a single oral dose of 50 mg/kg bw melatonin (equivalent to 3000 mg for a 60 kg person) pre-surgery reported no signs of adverse effects or post-operative complications associated with melatonin.

A study in which 4 women and 7 men (in- and outpatients) with Parkinsonism were given increasing daily doses of melatonin with maximum doses in the range 3000 – 6600 mg/d for 15 – 35 days reported headache, diarrhoea, flushes, abdominal cramps, scotoma lucidum (flashes of light in the eyes); there were no clinically significant changes to haematology and blood chemistry.

A recent review of the safety of melatonin in humans noted that 2 small studies in which oral dose of ~ 1000 mg melatonin were taken for 4 weeks reported no serious adverse effects; the Applicant does not consider the transient sedation observed in one of the studies to be serious. The second study indicated that melatonin depressed LH and growth hormone though the study involved 5 subjects. also noted that a cross-over study in which 12 healthy male subjects were administered placebo or 10 or 100 mg melatonin *i.v.* did not observe adverse effects on simple reaction times or self-reported adverse effects.

Based on the above information, [Section 4.9 of the proposed SmPC](#) for the Applicant's product notes that drowsiness, headache, dizziness, and nausea are the most commonly reported signs and symptoms of overdose with oral melatonin, that ingestion of daily doses of up to 300 mg melatonin did not cause clinically significant adverse reactions, and that flushes, abdominal cramps, diarrhoea, headache and scotoma lucidum have been

reported after ingestion of extremely high melatonin doses (3000 – 6600 mg) for several weeks. It is also noted that clearance of the active substance is expected within 12 h of ingestion¹²⁵.

Ability to drive or operate machines

A crossover RCT in which 5 mg IR melatonin was ingested at 12:30 hr by 16 healthy subjects (10 men, 6 women, mean age 22 years) observed impairment of task tracking and of response and reaction time scores for visual tasks, with the degree of impairment inversely correlated with saliva melatonin concentration (a good surrogate for plasma level) (). It was concluded that daytime administration of melatonin can impair neurobehavioural performance.

A crossover RCT () found administration of 5 mg IR melatonin at 17:00 hr to 8 men (23 – 28 years) to reduce alertness over the subsequent 4 h by ~ 30%, with a comparable effect seen in each subject.

When measured 1 h after ingestion of 10 mg melatonin by 14 healthy subjects (5 men, 9 women, mean age 28 years) in the late morning, posturographic performance (the contribution of visual information to balance) was decreased in all subjects, with 6 subjects showing impaired eye movements (). Improvements in some parameters were also seen in some subjects. None of the subjects reported fatigue, drowsiness, dizziness or other side effects. It was concluded that melatonin interacts with vestibular reflexes, causing specific impairment of oculomotor and postural performance.

A crossover RCT specifically designed to examine the effect of melatonin on driving performance collected data via a clinical examination, body-sway test, and a standardised driving computer test battery (assessing attention, reaction time, concentration and sensomotor coordination), and for subjective sleepiness, for 20 healthy subjects (12 men and 8 women aged 21 – 57 years) starting 1 h after ingestion of 5 mg IR melatonin at 16:30 hr (). Overall, the driving test battery showed no objective adverse impact of melatonin on driving performance, and the clinical examination results and body-sway test were unaffected. The subjective sleepiness expressed by the participants did not cause practically relevant impairment of driving performance, though the authors considered it grounds to recommend that caution should be exercised when driving under the influence of melatonin.

() found 2 mg melatonin (prolonged release) to exacerbate the adverse effects of zolpidem on psychomotor function and driving performance. This study is addressed in () [Pharmacodynamic drug interactions](#).

[Section 4.7 of the proposed SmPC](#) notes that melatonin has moderate influence on the ability to drive and use machines; as melatonin may decrease alertness for several hours, use of the Applicant's product duct is not recommended prior to driving or using machines.

Pharmacodynamic drug interactions

A RCT [REDACTED] investigating the efficacy for treatment of jet-lag of a 5 mg oral dose of IR melatonin, a 10 mg dose of zolpidem, and their combination, taken in-flight (17:00 – 21:00 hr) and at bedtime on 4 consecutive days after arrival found the combination to result in a significantly higher incidence of morning sleepiness, nausea, and confusion (particularly on the first day of arrival), and to reduce activity during the first hour after getting up, compared to melatonin or zolpidem alone when symptoms of jet-lag were graded by the participants (137 men and women, 18 – 68 years) each evening. Adverse events (including nausea and confusion) were generally comparable in nature and frequency in the zolpidem and combination groups (see [REDACTED] and as essentially no adverse events were reported by the melatonin group, the adverse events data do not suggest that melatonin exacerbated adverse events due to zolpidem. However, drop-out rate was higher in the combination group (11 of 40) compared to the melatonin group (5 of 40) and the zolpidem group (6 of 40).

Co-administration of a single oral dose of 2 mg melatonin (prolonged release) with zolpidem 10 mg at ~ 20:00 hr to 12 men and 4 women (55 – 65 years) exacerbated the adverse effects of zolpidem on psychomotor function, driving performance 1 h and 4 h post-dosing, and early memory recall ([REDACTED]). As plasma C_{max}, T_{max}, and AUC for each drug alone did not differ significantly from those measured for the drugs when given in combination, the authors suggested a pharmacodynamic interaction between melatonin and zolpidem (involving GABA-A receptors) that resulted in enhancement of the acute sedative effects of zolpidem by melatonin. The effects were short-lived, and [REDACTED] did not expect any hangover effects on cognitive function the following morning that would impair the ability to conduct the activities of normal living.

The findings of the 2 studies differ in relation to the potential for the interaction between zolpidem and melatonin to affect next-morning status. However the studies did not examine the same parameters, and the subjects in the study of [REDACTED] were also affected by jet-lag. Although zolpidem (an imidazopyridine) is structurally unrelated to benzodiazepines, it binds the same receptor (i.e. GABA-A). The presence of GABA-A receptors in the SCN raises the possibility that its function may be influenced by zolpidem, which may in turn modulate the action of melatonin on the SCN.

Text under the *Pharmacodynamic interactions* heading of [Section 4.5 of the proposed SmPC](#) notes that melatonin may enhance the sedative effect of benzodiazepines (e.g. midazolam, temazepam) and non-benzodiazepine hypnotics (e.g. zaleplon, zolpidem, zopiclone), and that in a study of jet-lag therapy the combination of melatonin and zolpidem resulted in a higher incidence of morning sleepiness, nausea, and confusion, and reduced activity during the first hour after getting up, compared to zolpidem alone.

[REDACTED]

[REDACTED] *Analgesic effects* (Secondary Pharmacodynamics and safety pharmacology) summarised information on the apparent analgesic action of exogenous melatonin. The underlying physiologic mechanisms were considered unclear [REDACTED] though the involvement of GABA-B receptors was named as one of several possibilities. This raises the possibility for pharmacodynamic interaction with GABAergic drugs such as opioidergic drugs (morphine, fentanyl) and diclofenac, and the potential for excessive analgesia. Several of the studies included in the reviews summarised in [REDACTED] noted that peri-operative intake of melatonin was associated with reduced post-operative intake of the above drugs, though the issue of whether this apparent pharmacodynamic drug interaction could have adverse effects, such as excessive

analgesia, was not addressed. Safety reviews of melatonin summarised in [REDACTED] [Reviews addressing melatonin safety](#) have not raised relevant concerns.

The above data suggest that oral doses of melatonin comparable to the recommended dose for the Applicant's product have an analgesic action, though analgesic, sedative, and eventual anxiolytic effects may, in fact, contribute to the efficacy of melatonin taken at bedtime for treatment of jet-lag. Considering the posology and brief duration of a treatment period proposed for the Applicant's product, the apparent analgesic effect of melatonin is not considered a safety concern.

[REDACTED]

A study in which 2 mg melatonin (prolonged release) was taken by 36 Type 2 diabetics (25 women, 11 men; 46 – 77 years; 16 on oral hypoglycaemic agents, 20 on insulin) for 3 weeks in a controlled phase, and for a further 5 months in an open phase, stated that no interaction with any of the medications frequently used by diabetic patients was observed (i.e. metformin, sulfonylureas, thiazolidinediones, peroxisome-proliferator activated receptors agonists, insulin, fibrates and other lipid-lowering agents, angiotensin-converting inhibitors, calcium antagonists, beta-blockers, anticoagulants, and serotonin-reuptake inhibitors) [REDACTED]

The potential for oral melatonin to transiently impair glycaemic control when taken in close proximity to a meal, its implications for diabetics, and relevant safety information included in the proposed SmPC is addressed in [Section 2.5.5.6.2 Adverse effects on glycaemic control](#) (Specific safety issues).

Nifedipine and other calcium channel blockers

As noted in section [REDACTED] melatonin is suspected of interacting with calcium channel blockers (e.g. nifedipin), with melatonin treatment potentially leading to a general increase in BP in hypertensive patients treated with antihypertensive drugs. Moreover, *in vitro* and animal studies have observed modulatory effects of melatonin on calcium-channel activity [REDACTED] suggested to be a result of competition for the same calcium channels [REDACTED] although the exact mechanisms behind this interaction in the treated hypertensive patients remain unknown. As a consequence, a warning about the possible interaction of melatonin with Nifedipine and other calcium-channel blockers has been added to *Pharmacodynamic interactions* of [Section 4.5 of the proposed SmPC](#).

Warfarin

The Cochrane review of melatonin for jet-lag ([REDACTED] updated 2008) summarised 6 adverse drug reaction reports involving concomitant intake of melatonin and warfarin: prothrombin time was increased in 3 of the reports and decreased in 3. The lack of a plausible PK mechanism to explain these divergent effects was addressed under the heading *Warfarin* in [REDACTED] [Drugs not considered to affect melatonin metabolism](#). Likewise, a plausible pharmacodynamic mechanism is not apparent, and it was not identified as a potential safety issue in reviews of the safety of melatonin (e.g.

██████████ However, a small scale non-RCT reported that prothrombin time was increased in 8 of 10 patients taking both melatonin and warfarin, making the authors suggest that the anti-coagulation efficiency of warfarin could be impacted by melatonin ██████████. The study did suffer from a range of issues, such as the small scale, short monitoring period, no control group, and varying doses of warfarin given during the observation period, making the supposition controversial. This notwithstanding, and considering that a study has shown decreased levels of factor VIII and fibrinogen upon single dosing treatment with 3 mg oral melatonin ██████████, a warning about the possible impact of melatonin on warfarin's blood clotting effects has been added to *Pharmakodynamic interactions* of [Section 4.5 of the proposed SmPC](#).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Prostaglandin synthesis inhibitors (NSAIDs) such as acetylsalicylic acid and ibuprofen, taken in the evening, may suppress the night-time release of endogenous melatonin levels ██████████. The following precaution has been added to *Pharmakodynamic interactions* of [Section 4.5 of the proposed SmPC](#): If possible, administration of NSAIDs should be avoided in the evening.

Beta-blockers

Beta-blockers may suppress the night-time release of endogenous melatonin and should therefore be administered in the morning. Night-time exogenous melatonin administration may be a beneficial treatment for sleeping disorders in beta blocker patients ██████████. A precaution summarising the above has been added to *Pharmakodynamic interactions* of [Section 4.5 of the proposed SmPC](#).

██████████

██████████.

Potential “*Off-label use in children under 2 years of age*” has been added as an important potential risk in the product's RMP.

2.5.6 BENEFITS AND RISK CONCLUSIONS

An oral dose of melatonin (immediate-release) in the range 2 – 6 mg has, depending on the time of day at which it is taken, the capacity to shift (advance or delay) the daily pattern of endogenous melatonin synthesis. The rhythmicity of endogenous melatonin production – which modulates the diurnal rhythm of many body processes – is disturbed in a number of circadian rhythm disorders, including jet-lag. Jet-lag is a consequence of the body's internal clock (and diurnal rhythms) not being synchronised with local (destination) time due to rapid travel across time zones. Alleviation of jet-lag is of importance for business people, military personnel, and others required to perform complex tasks after arrival, and to athletes and others required to perform physically. However, it is also relevant for holidaymakers due to the potential for jet-lag to interfere with vacation activities.

Clinical studies, and analyses of their pooled data, have demonstrated that ingestion of immediate-release melatonin (0.5 – 8 mg, typically 5 mg) at bedtime on arrival at destination for 4 – 5 days reduces subjective ratings of overall jet-lag (by ~ 42%) and the duration of jet-lag (by ~ 33%). As people generally find it harder to shorten their day (i.e. advance their body clock) eastward travel (which requires such adjustment) is generally associated with more severe jet-lag, though melatonin appears similarly effective for jet-lag following travel in an eastward or westward direction. These findings are based on data for adult men and women, including elderly persons; children and adolescents have not been adequately studied in relation to efficacy in relation to treatment of jet-lag. Consequently, the Applicant's product is not recommended in persons under 18 years for the treatment of jet-lag. Experts, organisations and authorities have issued opinions, guidelines and posology recommendations for melatonin for the treatment of jet-lag.

Jet-lag is a transient disorder, and the maximum recommended duration of use of the Applicant's product is 5 days, with the recommendation that the dose that adequately alleviates symptoms is taken for the shortest period. When taken on a daily basis for up to a week, typical therapeutic doses of melatonin have a very good safety profile. Safety data from studies of melatonin for jet-lag, in other circadian rhythm disorders, and in safety studies indicate that the adverse events reported most commonly are sleepiness / drowsiness, headache, dizziness / disorientation, and nausea, though their frequency is low and often comparable to that in subjects receiving placebo. Effects on routine clinical chemistry-, haematology and endocrine parameters are rare, and are typically mild and transient. No serious adverse effects were associated with ingestion of typical therapeutic doses of melatonin in the individual studies. These findings are supported by reviews addressing specific and general aspects of melatonin safety. Even ingestion of an extreme, single dose of melatonin by adults is generally safe, with the above adverse effects the most common signs and symptoms of overdose.

Data for long-term use (many months to years) of melatonin by adults are limited; such data is more extensive for children and adolescents, though specifically designed long-term safety studies are lacking. Knowledge of the manner in which endogenous melatonin level modulates (activates or suppresses) the hypothalamic-pituitary-gonadal axis in mammals, and animal studies showing that *in utero* and post-partum exposure to melatonin can delay or advance sexual development and potentially affect reproduction, raise the possibility of comparable effects in humans. Importantly, no evidence for such effects in human children and adolescents have been seen in studies. However, with regards to pregnant or lactating women, or women or men planning a pregnancy, the Applicant's product is not recommended.

As melatonin causes sleepiness / drowsiness, it may affect alertness for several hours and thus pose a risk in relation to driving or using machines. Limited data suggests that

melatonin taken in close proximity to a meal can transiently impair glycaemic control. Appropriate warnings are included in the proposed product information. Other safety concerns are limited to minor patient groups, namely persons with or predisposed to seizures or autoimmune disorders; these concerns are addressed in the product information (PI: SmPC, PIL). As melatonin is primarily metabolised in the liver, and its metabolites primarily excreted by the kidneys, warnings regarding severe renal or hepatic impairment are included in the PI.

Melatonin is metabolised mainly by CYP1A enzymes, primarily CYP1A2, thus pharmacokinetic interactions with other drugs and substances metabolised via these routes are possible. A number of documented or probable interactions are named in the PI; caution is recommended in a number of cases, though there are no contraindications. The effect of other drugs on the metabolism of melatonin is not expected to pose a serious risk due to its low toxicity and since appropriate warnings have been included in the PI.. The PI notes that melatonin may enhance the sedative effect of benzodiazepine and non-benzodiazepine hypnotic, and increases the incidence of adverse effects associated with zolpidem.

Melatonin has limited potential for tolerance, dependence, and withdrawal. Longer-term use (e.g. for periods of insomnia) is a potential situation for misuse, though the risk of harmful effects of such use is considered limited.

As outlined in section 1.6 the product is not expected to pose a risk to the environment.

Overall the benefit-risk balance is considered favourable for use of the Applicant's product for short-term treatment of jet-lag in adults.

In conclusion, when used in accordance with the proposed product information, Melatonin 3 mg film-coated tablets is considered to be an effective treatment for jet-lag and not to constitute a significant risk to users, society, or the environment.

[REDACTED]

2.5.7 LITERATURE REFERENCES

